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Studying the safety of drugs in pregnancy: and the gold standard is...

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ABSTRACT

Pregnant women are often advised not to take any medication as it might have adverse effects on the fetus and possibly in the future on an infant or developing child. However, for many women who are diagnosed with a chronic illness, discontinuing their medication is not an option. Women may also require treatment for acute illnesses, such as infections with a high fever, which may compromise the fetus if not treated. However, studying the safety of drugs during pregnancy is fraught with limitations, mostly because of ethical reasons, as obviously no pregnant woman is going to volunteer to participate in a randomized controlled trial (RCT). In the absence of RCTs, which are the gold standard, we have to rely on observational studies, which are usually in the form of case reports, case series, chart reviews, cohort studies, case-control and nested case-control studies, and administrative database studies. In this review, the various methods of studying drug use in pregnancy are described with their accompanying strengths and weaknesses and supported by examples from the literature to illustrate each method. In conclusion, it appears that a combination of methods may be used to provide evidence-based information to assist an expecting woman, together with her health care provider, in making an informed decision as to whether or not the use of a particular drug is appropriate during pregnancy.

Key words

Drug evaluation studies; Epidemiologic research designs; Pregnancy

RÉSUMÉ

On conseille habituellement aux femmes enceintes de ne prendre aucun médicament dans le but d'éviter la survenue possible d'effets indésirables chez le fœtus, le nouveau-né et chez l'enfant au cours de son développement ultérieur. Il n'est cependant pas indiqué d'arrêter le traitement chez beaucoup de femmes souffrant d'une maladie chronique. Par ailleurs, l'absence de traitement chez une future mère souffrant d'une maladie aiguë, comme une infection ou une fièvre élevée, peut compromettre le développement de son fœtus. L'étude de la sécurité des médicaments durant la grossesse souffre malheureusement de limitations principalement pour des raisons éthiques, à savoir l'impossibilité des femmes enceintes à participer volontairement à des études contrôlées randomisées. Suite à l'absence de ce 'gold standard' nous devons utiliser l'information d'études observationnelles comme les reports de cas, séries de cas, revue des registres, études de cohortes, étude cas-témoin au sein d'une cohorte, et études de bases de données médico-administratives. Au cours de cette revue, les différentes méthodes d'étude des médicaments durant la grossesse sont décrites avec leurs forces et leurs faiblesses, étayées d'exemples de la littérature pour illustrer chacune de ces méthodes. En conclusion, il apparaît que la combinaison de différentes méthodes d'étude peut être utilisée pour procurer une information basée sur l'évidence aux femmes enceintes et à leurs médecins pour prendre une décision correctement informée concernant l'utilisation d'un médicament durant la grossesse.

Mots clés

Études d'évaluation des médicaments; Méthodes d'investigation épidémiologiques; Grossesse

RESUMEN

Las mujeres embarazadas generalmente reciben la recomendación de no tomar ningún medicamento ya que podría tener efectos adversos en el feto y, más tarde, en el niño durante su desarrollo. Sin embargo, en muchas mujeres con enfermedades crónicas, la suspensión del medicamento no es una alternativa. Algunas mujeres podrían requerir tratamiento para algún problema agudo, como una infección asociada a fiebre, lo que podría comprometer al feto si la madre no recibe tratamiento alguno. Sin embargo, el estudio de la seguridad de los medicamentos en el embarazo está lleno de limitaciones, ya que por razones éticas ninguna mujer va a participar voluntariamente en un estudio clínico controlado. En la ausencia de este tipo de estudios, considerados como el estándar de oro, tenemos que apoyarnos de estudios observacionales, que son generalmente presentados en forma de reportes de caso, series de casos, revisiones de expedientes, estudios de cohorte, de casos y controles, de casos y controles anidados, o de bases de datos. En esta revisión, estos diferentes métodos de estudio de los medicamentos en el embarazo se describen junto con sus respectivas fortalezas y debilidades y con ejemplos de la literatura para ejemplificar cada método. En conclusión, parece que la combinación de métodos de investigación podría usarse para proporcionar información basada en evidencias para apoyar a las mujeres, junto con su médico, a tomar decisiones informadas sobre cuando usar un determinado medicamento durante el embarazo.

Palabras claves

Estudios de evaluación de los medicamentos; Diseños de investigación epidemiológica; Embarazo

INTRODUCTION

In the not so distant past, it was assumed that there was a “placental barrier” that prevented any agent from crossing the placenta and coming into contact with the fetus. Consequently, when women became pregnant, lifestyles changed little as they continued to smoke cigarettes, drink alcohol and take medications. However, this practice changed dramatically following the thalidomide tragedy. This tragedy was a warning sign that changed the “placental barrier” thinking and set off alarms where today, almost any exposure is considered a potential teratogen. Before discussing the current models that are used to examine the safety of drug use in pregnancy, there are some points that need to be discussed, to allow an understanding of this field of research.

Pharmacokinetics of the maternal–fetal unit

Almost all drugs have been shown to cross the placenta and enter the fetal circulation in measurable quantities. However, it should be noted that only the free fraction of a drug is available to cross the placenta. Several models have been used to explain the maternal–fetal–placental unit in terms of its pharmacokinetics. Common to the vast majority of these models there are two main factors that contribute to pharmacokinetic changes due to pregnancy: 1) maternal physiological changes; and 2) the effect of the placental–fetal compartment.

These changes/factors, which include delayed gastric emptying, decreased gastrointestinal motility, increased volume of distribution, decreased drug binding capacity, decreased plasma protein levels (albumin), increased hepatic metabolism due to liver enzyme induction and increased renal clearance, can affect any or all drug absorption, distribution, metabolism and elimination. As such, the degree and nature of the changes in the pharmacokinetic profile of a given drug due to pregnancy are mainly dependent on the changes in metabolic pathways to which the agent is susceptible.

Recently, a large body of evidence has suggested that in late pregnancy there is substantial increase in the clearance rate of various drugs, due to increase function of different cytochrome P450 enzymes, including nicotine (2A6), fluoxetine and citalopram (2D6), and protease inhibitors (3A4). This could mean that women may need larger doses to achieve therapeutic steady state concentrations. Late pregnancy is also characterized by major changes in GFR, hepatic blood flow, protein binding and altered drug compliance. These changes lead, in most instances, to lower systemic exposure to drugs which are eliminated by both by the liver and kidneys [1].

Teratogenicity

Teratogenesis is defined as structural or functional dysgenesis of fetal organs and/or skeletal structures. The typical manifestations include: fetal growth restriction or death, carcinogenesis and physical malformations which may be of varying severity, requiring surgery in extreme cases. Also included are neurobehavioral abnormalities [2].

Fetal toxicity

Some drugs are not considered teratogenic but rather, embryotoxic. These agents are not considered to cause physical birth defects per se but are known to have deleterious health effects on the fetus following long-term exposure in utero. A prime example of a substance that is both teratogenic and embryotoxic is alcohol, which can cause physical defects when used in early pregnancy and adverse long term neurodevelopmental effects when used heavily throughout pregnancy [3].

STUDY OF DRUGS IN PREGNANCY

There are currently a number of models used to study the safety of drugs in pregnancy without performing RCTs, an unethical practice in pregnant women.

Case reports

These are considered a signal generator as they identify a potential problem, thus allowing a formal investigation if warranted. The major limitation of a case report is that it cannot be a causation, unless many other cases describe the same defect with the same exposure, as was the case in the thalidomide tragedy [4]. Of note, in the 46 years since that landmark case report was published, there has not been another one that has played such a major role in discovering a new teratogen. This is likely because since that time, pre clinical studies are far more rigorous, with the mandatory use of three different species in animal studies, as well as screening for signals in post marketing surveillance, either prior to or soon after the drug was introduced to the market. An example was in the case of isotretinoin, when even prior to its market launch, it was known from animal studies that it could be a teratogen, and was also found to be highly teratogenic in humans, in fact, more so than thalidomide [5].

Case series

In a case series, there can be several cases with up to hundreds or more. The main limitation of a case series is that there is no comparison group, so the results cannot be compared to a group representing the population. An example of a relatively large case series is 122 cases [6] where a small one would only have 4 cases [7].

Prospective, comparative cohort studies

In this model, used frequently by teratogen information services, exposures of interests are identified and a prospective follow up of women

are enrolled in the study, usually in the first trimester when organogenesis is occurring. Following birth of the baby, pregnancy outcomes are obtained and compared with other women who were not exposed to the drug in question or a teratogen and if possible a disease matched group. The strength of this model is the personal interview with the individual, which includes detailed history taking and whether she actually took the drug during pregnancy. Another strength is the prospective approach, when a woman is enrolled in the study she is in early pregnancy, so the outcome is unknown. It also allows for a comparison between the exposed and non-exposed group (i.e., baseline rates) of major malformations, spontaneous abortions, etc.

The major limitation of this model is the sample size, most often about 150 cases, which is small for statistical purposes as it only has an 80% power to detect a fourfold increase in major malformations. Approximately 800 cases in each group would be required to detect a twofold increase in risk of relatively common malformations and thousands of cases would be required to detect rare malformations. Another major limitation is that samples are not randomly selected as women calling a teratogen information service (the majority of instances where this model is used) and do not necessarily reflect the general population. Women who participate in this type of research, generally are in a higher socioeconomic class and are generally more motivated to do the "right things" to have a healthy baby. These studies can be conducted collaboratively with other similar groups worldwide, as in the case of a study recently published on the safety of mirtazepine (n= 104) in pregnancy, with no increase risk for major malformations, but increased risk for spontaneous abortions [8]. On the other hand the cases can come from a single program, as in the case of a study (n= 176) published on ondansetron, with no reported increase for any adverse effects [9].

Case control studies

These are retrospective studies where the outcome is known and the group is compared to another group who had the same outcome (in this area of study, the offspring were born with the same birth defects). The two groups are then matched on important variables and a search is conducted for evidence of exposure. This methodology is often used in teratology studies because far fewer cases are required to find rare birth defects, compared to prospective comparative cohorts. The main

limitation is the retrospective bias and the inability to not always be able to match for confounders. A couple of important studies that have been published using this model are a group who assessed associations between first-trimester maternal use of SSRIs and the risk of birth defects among 9,849 infants with and 5,860 infants without birth defects participating in the Slone Epidemiology Center Birth Defects Study: In analyses of defects previously associated with SSRI use (involving 42 comparisons), overall use of SSRIs was not significantly associated with an increased risk of birth defects [10]. Another group, using data derived from a population-based case-control study that included cases of orofacial clefts (n = 662), conotruncal heart defects (n = 207), neural tube defects (n = 265), and limb reduction defects (n = 165) found that corticosteroid use was associated with an increased risk for isolated cleft lip with or without cleft palate (odds ratio 4.3, 95% confidence interval 1.1-17.2) and isolated cleft palate (odds ratio 5.3, 95% confidence interval 1.1-26.5) [11].

Meta-analysis

This is a very useful method when studying drug use in pregnancy, as most observational pregnancy outcome studies have small sample sizes. This is a way of combining results across different studies, enlarging the sample size, so as to make a more definitive statement regarding safety/risk of the drug. Usually a minimum of at least two reviewers independently search for studies published in the literature on the drug of interest. A literature search is conducted by these two individuals, using all available data bases. Case-control and cohort studies are both accepted for analysis, as well as abstracts presented at scientific meetings, as long as the subjects were similar. The inclusion and exclusion process is then carried out by the two reviewers, who independently evaluate the articles for acceptance into the study. If necessary, a third reviewer may act as an adjudicator for any unresolved disputes.

The reviewers then extract the data from the included studies into 2x2 tables and the data is analyzed. The first meta-analysis carried out using pregnancy outcome data studies and birth defects was performed for Bendectin (doxylamine/pyridoxine), a drug used for the treatment of nausea and vomiting of pregnancy (NVP). This was prompted by several lawsuits against the company alleging that this drug was a teratogen. Eventually the company withdrew it from the market due to financial collapse as a

result of defending lawsuits, none of which were ever won by a plaintiff against the company. It was estimated that at one time 30 million women were exposed to this drug in the US and 25 epidemiologic studies had been performed regarding its safety during pregnancy. Following the combination of all the studies, with more than 17,000 women, there was no increased risk for major malformations [12].

Because this is a useful tool for evaluating conflicting evidence, many of the meta-analysis on pregnancy outcome and the safety of drugs have been performed for this reason. Another important meta-analysis was conducted that examined the use of corticosteroids and oral clefts because there was a discrepancy between data from a prospective cohort study and a case control study, with the prospective study not finding an increased risk and the case-control study finding an increased risk. Following synthesis of all the available data, the meta-analysis did find a small increased risk [13].

Administrative data base studies

Databases are not typically set up for pharmacoepidemiologic research as they are primarily developed for various administrative claims payment. For this reason, important data is often missing, especially for studies of drug use and pregnancy outcomes. However, they often contain large numbers of individuals with important information, so have been increasingly used in research, most frequently to conduct post marketing surveillance. Due to the extremely large sample sizes, there can be a potential for false positives as many statistical tests are used and the larger the sample size, the higher the probability of chance findings of statistically significant results with no clinical relevance. In addition, results are usually given in Odds Ratios (OR) and the baseline rate is rarely documented. For example, it is not very meaningful if, after comparing the results of two groups, there is a statistically significant OR, if the risk in both groups is below the baseline rate of what is expected in the population. In a recent publication, researchers examined the quality of 100 abstracts from published studies that had examined the safety of various drugs in pregnancy. In 94% of the results, when a significant OR was reported, or even if not, baseline rates were not documented [14].

Pregnancy registries

Pregnancy registries vary somewhat in design, which is important when examining their results.

They consist of voluntary reporting by either the women or by their health care providers and contain varying levels of data. Some registries are driven by pharmaceutical companies (often compelled by national or international drug licensing agencies) and provide data on pregnancy outcome related to the sponsor's own product. Others are organized by independent research groups and they can be more useful as comparative data is used. The major strength of these registries is that often they will contain prospective data, although some do report on retrospective data, they often contain large numbers of exposed women and can be run for several years. The limitations include the lack of comparison groups, as well as some confounders that are not available, such as alcohol and tobacco use, and concomitant drug use. There have been a number of studies that have been published using these data including a large study from GSK with more than 1,200 women exposed to bupropion in pregnancy, who were compared to another group of women exposed to other antidepressants [15]. There are several worldwide epilepsy registries that have been run for quite a number of years by both industry and academia [16].

Prescription data base studies

These studies are compiled using data from prescriptions that have been filled by the patient. The main strength of this method is the very large sample sizes. However, there are several limitations, the main one being that it is only known if a person filled the prescription, not that the drug was actually taken. Another limitation is that the collection of data is usually retrospective in nature. One group of researchers conducted a nested case-controlled study, where they separated a small group within a very large cohort and compared the rates of anomalies. This group did not find an increase risk for major anomalies [17]. However, another group also published a study on the safety of antidepressants in general where they found an increased risk for different malformations. There was no pattern of defects, there was no separation between major and minor malformations and there was no discussion of potential confounders [18].

National birth registries

Some countries, mostly in Europe, operate registries where the mother and child pairs are entered after birth and are followed up prospectively. Many studies have been published with data from The Swedish Birth Registry [19]. The Hungarian Case-Control Surveillance System of

Congenital Abnormalities is another group in this category who have published many pregnancy outcome studies following exposure during pregnancy [20].

When practicing evidence-based medicine, in the absence of randomized controlled trials (RCTs) which is Level 1, all of these methodologies loosely fit into the category Level II-2 [21]: "Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group."

SUMMARY

Studying the effects of drug use in pregnancy is a complicated process with currently no ideal model for conducting studies. Because of the ethical issues surrounding pregnancy and conducting an RCT, it is highly unlikely that there ever will be an ideal model. All of the models we are using have their limitations, such as small sample size, retrospective bias, inability to know exactly if the women took the medication in pregnancy and other missing data. However, this does not mean that the data collected is not valuable and useful to provide evidence-based information. Women and pregnancy is a highly sensitive topic with health care providers, with the media being very interested and eager to report findings, especially if adverse effects are reported [22]. Consequently, it is of great importance when translating results, to point out the limitations of each study and how it may affect the results. For best evidence, a combination of these different types of observational studies will assist women and their health-care provider in making informed decisions as to whether or not to take a particular drug during pregnancy.

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CONFLICT OF INTERESTS/DISCLAIMERS

A E is member of the Editorial Board of the journal.

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