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The advances in dealing with the safety of medicated drugs in pregnancy

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Abstract: The Japan Drug Information Institute in Pregnancy (JDIIP) was established with the aims of providing information on drug safety to women who are worried about drug use during pregnancy and creating evidence through epidemiological studies based on counseling cases. Since being established, JDIIP has made many contributions to the wellness of mothers and children by promoting the proper use of drugs during pregnancy. A network consisting of Core hospitals in 47 prefectures plays an important role in providing information for women living anywhere in Japan. Because cases of exposure to drugs whose safety we want to analyze are usually rare, networks of domestic and foreign teratology information services are necessary in order to produce high-quality evidence. JDIIP has been contributing to the education of pharmacists and doctors and to the creation of clinical practice guidelines in various medical societies by using keywords such as "pregnancy" and "medication". Future issues include creating an environment that is easily accessible for those seeking consultation, building a mechanism that makes it easy to create a basis for safety, and aiming for the continuing development of the organization.

***Keywords*:** drug safety, pregnancy, counseling, epidemiological study

Introduction

The thalidomide tragedy led to persistent concerns that using drugs during pregnancy causes fetal congenital anomalies. This has led to negative behaviors in women who are undergoing drug therapy for existing conditions, such as avoiding becoming pregnant or discontinuing necessary medications during pregnancy. There have been incidents of abortion among women who used drugs without realizing they were pregnant. Skilled counseling based on evidence is needed to relieve these anxieties. However, there were few skilled counselors and little quality evidence required for counseling in this field. The only safety-related evidence available when new drugs are launched is derived from animal studies. However, the results of these studies are not necessarily applicable to humans. Evaluation of risks during pregnancy should in principle be based on epidemiological research.

It became clear that counseling and epidemiological research systems were needed. To address these problems, the Japan Drug Information Institute in Pregnancy (JDIIP) was founded as a teratology information service (TIS) by the Ministry of Health, Labour and Welfare (MHLW) in 2005 at the National Center for Child Health and Development (NCCHD). Prior to opening, we received guidance from both Toranomon Hospital which had already started a Counseling Clinic for "Pregnancy and Medicine" in 1988, and also The MotheRisk Program (MRP) which was established at the Hospital for Sick Children (Toronto, Canada) in 1985 (*1*).

Besides MRP, several TIS were also established in Europe and North America. The European Network of Teratology Information Services (ENTIS) is made up of 17 TIS locations in Europe, starting with TIS, which was opened in 1990 in Milan, and 5 other TIS located in Asia and South America including JDIIP (*2*). The Organization of Teratology Information Specialists (OTIS), founded in the United States in 1999, consists of many members, including JDIIP members, and has published many papers through multicenter research. In 2013, OTIS announced MotherToBaby, a name for its public-facing service and research studies (*3*).

The Nordic countries have generated high-quality evidence of drug safety during pregnancy using personal identity number systems and midwifery interview systems (*4*).

Services provided by JDIIP (What does it do?)

The three main services provided by JDIIP are counseling regarding the safety of drug use during pregnancy, establishing evidence regarding the safety of drug use during pregnancy based on counseling cases, and recommending revisions of drug package inserts based on risk-benefit considerations in pregnant or nursing women. The medical staff of JDIIP consists of pharmacists and physicians, the latter of whom specialize in obstetrics, internal medicine, or neonatology (pediatrics). In addition, specialists in congenital anomalies are involved as consultants.

Counseling

JDIIP provides consultations for women who are concerned about the safety of drug use during pregnancy. At a meeting of experts prior to the foundation of JDIIP, face-to-face counseling was instructed for women taking high-risk drugs. Accordingly, core hospitals were designated in 47 prefectures nationwide, including the NCCHD Hospital, and consultation is now provided by "outpatient clinics for pregnancy and drugs" at these core hospitals (Figure 1).

In principle, we provide counseling based on epidemiological data by weighing risks and benefits. The original JDIIP safety information that is used in counseling is referred to as the "JDIIP-Summary". It was prepared by scrutinizing and summarizing information from a source often referred to as "Briggs" (*5*), a book compiling epidemiological studies on the safety of drugs during pregnancy, as well as databases of third-order information including Reprotox (*6*), the Teratogen Information System (TERIS) (*7*), and MRP (*1*) (Figure 2). The disadvantage of these third-order databases is that the data are not updated on a real-time basis. Therefore, in every consultation, JDIIP checks Medline or the information published by pharmaceutical companies and adds necessary information, if any. For drugs developed in Japan that are not available in English-speaking countries, there are almost no epidemiological data regarding their use during pregnancy. In such cases, JDIIP searches Japan Medical Abstracts or retrieves Interview Forms and makes inquiries to pharmaceutical companies if necessary (Figure 2). In order to ensure that the information JDIIP provides is correct, meetings of the JDIIP-Summary Review Committee, which includes external members, are regularly hosted by the department in charge at the MHLW.

There are three consultation methods: *i*) counseling at the "outpatient clinics for pregnancy and drugs" at the core hospitals mentioned above, *ii*) explanations provided by physicians who are treating clients based on the safety information sent from the office, and *iii*) counseling over the phone by medical staff members of JDIIP. Upon receiving the questionnaire, the office arranges a consultation method based on the preference of the client and the characteristics of the drugs concerned. From October 2005, when JDIIP was founded, to November 30, 2020, there were 15,601 consultations (6,276 before conception and 9,455 during pregnancy) regarding the use of drugs during pregnancy, and 7,434 consultations regarding the use of drugs during breastfeeding. We demonstrated that the counseling provided by JDIIP is effective because it reduces the anxiety in women

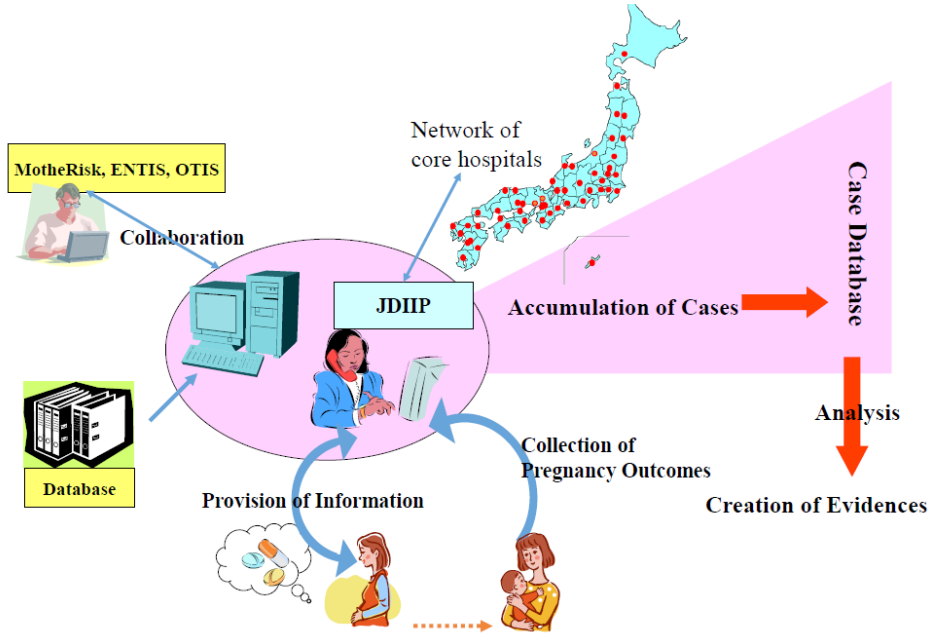

Figure 1. Japan Drug Information Institute in Pregnancy (JDIIP). The main tasks of JDIIP are counseling and establishing evidence regarding the safety of drug use during pregnancy. The core hospitals were designated in 47 prefectures nationwide and consultation is provided by "outpatient clinics for pregnancy and drugs" at these core hospitals.

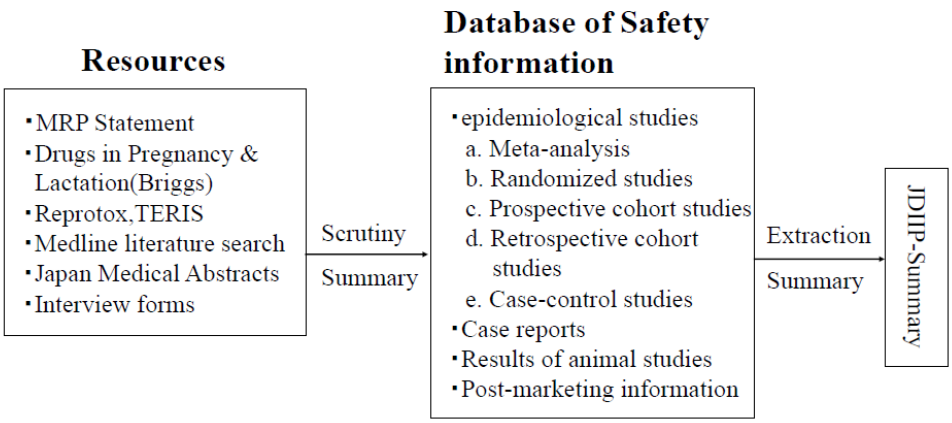

Figure 2. Method for preparation of information to be provided. The original JDIIP safety information that is used in counseling is referred to as the "JDIIP-Summary". It was prepared by scrutinizing and summarizing the information from third-order databases such as "Briggs" (*3*), Reprotox (*4*), TERIS (*5*), and MRP (*6*). Furthermore, in every consultation, Medline or the information published by pharmaceutical companies are checked.

who are using drugs during pregnancy. This resulted in increased deliveries for women, who would otherwise hesitate to continue pregnancy due to excessive concern about drug risks (*8*).

Generation of evidence

The medical questionnaire completed by clients includes columns for the names of relevant drugs, their doses, and their indications. Consultees are also asked to provide their age, height, body weight, history of folic acid intake, and history of pregnancy, as all of these can be confounding factors regarding safety. For consultations during pregnancy, JDIIP sends clients a survey card 1 month after the expected delivery date asking them to provide the results of pregnancy and the presence or absence of congenital abnormalities. Based on this approach, JDIIP requested that 9,455 pregnant women who consulted JDIIP from October 2005 to November 30, 2020, participate in a survey of pregnancy results; 8,378 women provided consent, and 6,816 returned their survey cards. The response rate was 81.4%, which is considered to be relatively high among studies in this field. In this way, JDIIP established a methodology for safety analysis based on information regarding drug use and pregnancy results, *i.e.*, for prospective cohort research starting from the time of consultation.

Using this methodology, JDIIP has analyzed several drugs and presented or published the results at academic meetings or in journals (*9,10*). In particular, the authors were the first worldwide to report on the safety of oseltamivir (*11*) during the outbreak of a new type of influenza. In order to assess if risks are unlikely, more than 300 cases exposed to a target drug are needed. For several years, JDIIP has been working on publishing evidence regarding drug safety during pregnancy with the combined data of JDIIP and Toranomon Hospital using public funding. It is hoped that this plan will show the safety of drugs developed in Japan for which evidence has thus far been scarce (*12*).

Recommendation regarding revision of package inserts

For almost all drugs that are contraindicated in pregnant women based on animal studies, the contraindication is not reversed even after the risk during pregnancy is ruled out based on epidemiological studies. That is to say, the use of these drugs continues to be avoided in the treatment of pregnant women who need them. Practice guidelines can solve this problem. While package inserts are prepared by pharmaceutical companies, practice guidelines are developed mainly by physicians. Confusion tends to occur in medical practice regarding which should be followed when there are discrepancies between them. To address this issue, MHLW started a project to promote the proper use of drugs in pregnant or nursing women in 2016. JDIIP is responsible for examining the data from animal studies and epidemiological research as well as those regarding clinical utility in cooperation with external experts, and submitting the results to the MHLW. As the first accomplishment of this project, the phrase "contraindicated during pregnancy" in the package inserts of immunosuppressants such as tacrolimus, cyclosporine, and azathioprine, was successfully changed to "can be used during pregnancy if needed" in 2018. Similar efforts are currently being made for calcium blockers.

Education and social responsibility (How does JDIIP contribute to society?)

Once a year, JDIIP offers seminars for physicians and pharmacists at core hospitals and organizes a public symposium on a timely theme. In addition, JDIIP provides educational lectures in response to invitations by academic associations, medical associations, and

pharmacist associations. Moreover, members of JDIIP have published multiple textbooks in this field. JDIIP is also involved in the development of practice guidelines at the request of academic associations, such as the Japanese Society of Nephrology, the Japanese Circulation Society, the Japan Society for Adult Congenital Heart Disease, the Japanese Society of Hypertension, the Japan College of Rheumatology, the Japanese Dermatological Association, and the Japan Society for Transplantation.

Future vision (What is JDIIP going to do?)

Counseling

The results of the Japan Environment and Children's Study indicate that 70% of pregnant women use drugs, including supplements (*13*). Moreover, the numbers of consultations over the phone and at outpatient clinics handled by the Teratology Information Service (TIS) of Korea, were 10,721 and 253 respectively in 2015 (personal communication). JDIIP is clearly far from fulfilling the needs of the Japanese population. It is suspected that the counseling service is not sufficiently utilized by the women who need it. To make the process even easier for users, the pre-counseling procedures should be simplified. Currently, JDIIP is considering an IT-based method for accessing the service. JDIIP is also planning to collaborate with pharmacists at core hospitals nationwide and at local pharmacies to increase awareness of methods for using the services offered by JDIIP (mainly through core hospitals) and to disseminate knowledge in this field.

Generation of evidence

Discussions regarding the use of drugs for chronic diseases during pregnancy are often held between patients and their physicians and do not frequently lead to consultations with JDIIP. Therefore, JDIIP needs to proactively include these drugs in its databases. Currently, several epidemiological research projects that use JDIIP as a platform for registry systems are underway. JDIIP and core hospitals will conduct registry surveys of certain drugs in collaboration with academic associations and research groups. JDIIP will also explore the coordination of its services with post-marketing surveillance by pharmaceutical companies.

International collaborative research is essential for achievement of high quality results in epidemiological studies, particularly in this area where it is difficult to gather information on existing cases. JDIIP has had contact with MRP, ENTIS, and OTIS, and recently started conducting joint research with them.

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