LEADING ARTICLE

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Monitoring Outcomes of Pregnancy Following Drug Exposure

A Company-Based Pregnancy Registry Program

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Abstract

Women who discover they are pregnant after exposure to a drug and pregnant women who have a condition that requires continued treatment during pregnancy are told to balance the benefits and risks of the exposure to justify continuation of treatment, discontinuation of treatment or, possibly, pregnancy termination. However, there are limited data available to inform decision-making. The Merck Pregnancy Registry Program is a company-run pregnancy registry whose objective is to acquire and analyse information on drug exposures and pregnancy outcomes to better describe the safety profile of Merck products used during pregnancy.

Information is collected from women and healthcare providers who call to report drug exposure during pregnancy. Prospective pregnancies are followed up to outcome and data are collected via questionnaires, telephone calls and a review of medical records.

Reports are classified as prospective (information received prior to knowledge of pregnancy outcome) or retrospective (received after the outcome is known). Congenital anomaly reports are assessed for timing of exposure, maternal age and medical history, biological plausibility and concomitant medication exposures. Rates of pregnancy outcomes and birth defects in the prospective cohort are computed and confidence intervals are calculated to reflect the strength of the finding based on the sample size. Rates of pregnancy outcomes in the Pregnancy Registry are compared with the rates of pregnancy outcomes in the general US population and, if available, in subpopulations with the relevant disease states.

The limitations of post-marketing surveillance are well known as voluntary reporting of individuals and healthcare professionals is known to be subject to various types of bias. Small sample size is another major limitation. However, the strength of the registry lies in its ability to gather pregnancy outcome reports early in the life of a product and to recognise and analyse unusual birth defects.

Our data suggest that pregnancy registries can be used to review human exposure data in a systematic fashion so that useful information can be shared with women and their healthcare providers. The use of the pregnancy registry

design has allowed for the collection and analysis of data on the effects of drug exposures on human pregnancies that have otherwise been difficult to obtain.

Evaluating the safety of product use during pregnancy has been a difficult task for the pharmaceutical industry. Animal reproduction studies are not always predictive of human response. Protocols contain strict requirements for the use of birth control methods to limit the number of unplanned pregnancies and inadvertent exposures during clinical trials. The number of pregnancies that do occur in studies is too low to reliably predict the effect of the exposure once the product is approved for use in the general population. Consequently, most products come to market with little human data available to guide clinical decisions regarding the continuation of an exposed pregnancy or the use of new products during pregnancy.

In 1995, Merck & Co., Inc. acquired licensure for VARIVAX® [1] (varicella virus vaccine live OKA/Merck), a vaccine that helps to protect against a potentially teratogenic virus, varicella zoster. Anticipating that the vaccine might be inadvertently administered during an unrecognised pregnancy, Merck, in conjunction with the US Centers for Disease Control and Prevention (CDC), established the Pregnancy Registry for VARIVAX®. The CDC has acted in an advisory role, providing assistance with registry design, review of anomaly reports, input on data analysis, and compiling the annual reports.

Since its inception, new Merck products with relatively high potential to be used by women of childbearing potential have been added to the Merck Pregnancy Registry Program, including montelukast (SINGULAIR®) for asthma, rizatriptan (MAXALT®) for migraines, and rofecoxib (VIOXX®) for pain and inflammation. Merck initiated these registries on a voluntary basis based on anticipated use by women of childbearing potential, not at the request of the US FDA or any other regulatory agency. Preclinical animal testing did not indicate potential teratogenicity in these products (see package circulars). In addition, Merck participates in the Antiretroviral Pregnancy Registry[1] for the protease inhibitor indinavir (CRIXIVAN®), one of 20 products included in this ongoing collaborative registry coordinated by Inveresk and sponsored by eight pharmaceutical companies.

The goal of the Merck Pregnancy Registry Program is to acquire and analyse information on Merck drug exposures and pregnancy outcomes (livebirths, spontaneous abortions, elective abortions, fetal deaths, congenital anomalies) to better describe the safety profile of products used during pregnancy.[2] This information is disseminated to healthcare professionals in annual reports to help them and their patients make informed clinical decisions and can be used to update product labelling. For example, the following statement has been added to the VARIVAX® Worldwide Product Circular: "In the first 6 years of the Pregnancy Registry for varicella vaccine (OKA/Merck), of 97 seronegative women and 315 women of unknown serostatus who received varicella vaccine during pregnancy or within 3 months before pregnancy, none had newborns with abnormalities compatible with congenital varicella syndrome".[3]

Pregnancy registries exist in various forms in the pharmaceutical industry, in the academic research environment[4] (see table I), and in some national reporting systems.[5] The FDA is encouraging the use of pregnancy registries and other research designs to better assess the risks of drug or biologic exposure during pregnancy.[6] Our 8 years of experience in this area warrants our sharing of information on the evolution of our Pregnancy Registry Program to assist other interested parties in establishing similar programmes.

1. Design of Merck Pregnancy Registries

The Registries are operated by the Clinical Risk Management Safety Surveillance (CRMSS) and

1 The use of trade names is for product identification purposes only and does not imply endorsement.

Table I. Programmes investigating exposure to therapeutic agents during pregnancy (December 2002)

Pregnancy registries	Medications	Source	Contact
Aldara Pregnancy Healthline	ALDARA™ (imiquimod)	Motherisk Program[a]	www.motherisk.org
Antiepileptic Drug Pregnancy Registry	Antiepileptic medications	Massachusetts General Hospital/ Genetics and Teratology Unit	www.massgeneral.org/aed
Antipsychotic Medicines During Pregnancy	Antipsychotic medications	Motherisk Program[a]	www.motherisk.org
Antiretroviral Pregnancy Registry	Antiretroviral medications	PharmaResearch Corporation for eight company sponsors[b]	www.apregistry.com
Asthma Medications and Pregnancy Project	Asthma medications	OTIS	www.otispregnancy.org
Cancer and Childbirth Registry	Chemotherapeutic agents	Cooper Health	www.cooperhealth.org/medical/ department/physicians/c/ cardonick_elyce.htm
GlaxoSmithKline Pregnancy Registries	Bupropion, lamotrigine, sumatriptan, naratriptan	PharmaResearch Corporation for GlaxoSmithKline Inc.	http://pregnancyregistry.gsk.com
Merck Pregnancy Registry Program	Varicella virus vaccine, montelukast, rizatriptan, rofecoxib	Merck & Co., Inc.	www.merckpregnancyregistries.com
National Transplantation Pregnancy Registry	Post-transplant medications	Thomas Jefferson University	www.tju.edu/ntpr
Neoral Pregnancy Registry for Psoriasis and Rheumatoid Arthritis	NEORAL® (cyclosporin)	Thomas Jefferson University	www.jeffersonhealth.org/tjuh/ neoralregistry
Rheumatoid Arthritis and Pregnancy Study	Rheumatoid arthritis medications	OTIS	www.otispregnancy.org
Zofran use during pregnancy	ZOFRAN® (ondansetron)	Motherisk Program[a]	www.motherisk.org

a Motherisk Program/Hospital for Sick Children, Toronto, ON, Canada.

b Sponsors of the Antiretroviral Pregnancy Registry include Abbott Laboratories, Agouron Pharmaceuticals Inc., Boehringer Ingelheim Co., Bristol-Myers Squibb Co., Gilead Sciences Inc., GlaxoSmithKline, F. Hoffmann-LaRoche Ltd, Merck & Co., Inc.

OTIS = Organization of Teratology Information Services.

Worldwide Product Safety & Epidemiology (WPS&E) Departments of Merck Research Laboratories. CRMSS and WPS&E perform post-marketing surveillance by collecting, reviewing and processing reports of adverse experiences (AEs) from healthcare providers and consumers. Inquiries from phone calls and field representatives are received at the Merck National Service Center (MNSC), where information is recorded and reports are forwarded to CRMSS and WPS&E. All reports of AEs and pregnancies that are temporally associated with exposure to a Merck product (i.e. they occurred shortly after or during treatment with a Merck product) are entered into the in-house database, the New Worldwide Adverse Experience System (NWAES).

To encourage calls to the registry, the following statement is included in the pregnancy section of the product circular for each product in the program: "Merck & Co., Inc. maintains a registry to monitor the pregnancy outcomes of women exposed to [product] while pregnant. Healthcare providers are encouraged to report any prenatal exposure to [product] by calling the Pregnancy Registry at 800-986-8999". Publications, presentations, a registry website, and mailings to professional organisations all are utilised to encourage reporting to and raise awareness of the registries and the annual reports.

Currently, reports of exposure during pregnancy are not reportable to FDA as single case reports unless there is an AE reported along with the exposure. Data on reports of exposure during pregnancy are included in periodic safety update reports (PSURs) that are regularly submitted to regulatory agencies worldwide. Merck forwards reports of serious, unexpected events to worldwide regulatory agencies within 15 days of receipt by the company. Reports of pregnancy losses (spontaneous abortion, late fetal death, elective termination), life-threatening developments (abruptio placentae, fetal distress), birth defects, and neonatal or maternal death are considered reportable. Since reports of exposure during pregnancy are received through the passive, spontaneous reporting system and may or may not be enrolled in a registry, they are considered spontaneous marketed reports for submission to the regulatory agencies.

Reports of exposure during pregnancy are reviewed to assess their eligibility for inclusion in the registry according to specific enrolment criteria. These criteria include: (i) exposure during pregnancy; (ii) residency in the US or Puerto Rico (and Canada for varicella vaccine); (iii) identification of a healthcare provider; and (iv) identification of a patient. Fulfilment of these four criteria is sufficient for the report to be considered 'enrolled'. For drug products, 'exposure during pregnancy' is defined as any product use since the first day of the last menstrual period (LMP). For live virus vaccines, because of the unspecified period of viraemia, 'exposure during pregnancy' means receipt of vaccine up to 3 months prior to LMP or at any time during the pregnancy. Non-enrolled reports follow routine procedures – standard pregnancy questionnaires are mailed to the healthcare provider at the time of the initial call and again at the expected date of delivery. For products in the registry, routine follow-up procedures and Pregnancy Registry procedures are concurrently initiated to ensure maximum data capture.

Most calls are made to the Pregnancy Registry following inadvertent exposure – the pregnancy was undiagnosed prior to use of the product. Many reporters call to ask if the drug company might have more information about the effect of the exposure on the fetus than what is included in the product label. Some callers are trying to make a decision about whether or not to terminate a pregnancy because of the exposure.

All reports of exposure during pregnancy are maintained in the company's NWAES database. Those enrolled in the registries receive additional intensive follow-up efforts. Attempts are made to respond to the reporter promptly upon receipt of the original report (preferably within 24 hours) as we are cognisant of the time-sensitive nature of pregnancy-related decisions and the anxiety that may accompany an exposure to an agent of unknown or perceived teratogenic potential. A telephone call is made to the healthcare provider if requested or if the

initial information obtained is insufficient or needs clarification. The registry data are reviewed and enrolment of the patient is discussed with the caller.

Healthcare providers who call or who are identified by their patients are sent a fax containing the initial pregnancy questionnaire, the outcome questionnaire, the patient consent form (available in English and Spanish) and an annual report describing our experience with the relevant product(s). Efforts have been made to streamline the data collection process so that participation in the registry is not overly burdensome to the healthcare provider. Questionnaires limited to one page collect essential information (see table II and table III for content). Initial questionnaires can be completed and faxed or mailed back to the Pregnancy Registry. Outcome questionnaires can be placed in the patient's chart for completion at the time of delivery or pregnancy outcome.

Because the registry often does not have direct access to the patients, the healthcare providers are asked to discuss the registry and the consent form with the patient. If the provider does not obtain informed consent but continues to provide information to the Pregnancy Registry, that information is accepted and entered into the NWAES database. Informed consent is encouraged in order to provide information to the patient, to decrease lost to follow-up and to obtain medical records. Consent is not required for reporting because the registry procedures are part of the post-marketing surveillance activities performed for voluntarily reported AEs.

Table II. Information requested for the Merck Pregnancy Registry Program: Initial Pregnancy Questionnaire

Healthcare provider information
Name, address, phone number, fax number
Primary care provider
OB/GYN
Disease-specific specialist
Patient information
Name, address or office chart number and date of birth
Race/ethnicity
Medication use during this pregnancy: dates of use, strength, indication
Current pregnancy information
LMP, EDD
Prenatal testing: test type, date, results, indication, comments
Pregnancy history
Previous pregnancy outcomes and prior birth defects

EDD = estimated date of delivery; **LMP** = last menstrual period; **OB/GYN** = obstetrician/gynaecologist.

Table III. Information requested for the Merck Pregnancy Registry Program: Pregnancy Outcome Questionnaire

Pregnancy outcome
Livebirth: date, sex, weight, weeks from LMP, normality (congenital anomalies, complications, abnormalities)
Fetal loss: elective termination, spontaneous abortion, late fetal death (date, weeks from LMP, examination of products of conception – if yes, description)
Obstetric information
Complications of pregnancy, labour and delivery, infections or illnesses during this pregnancy, concurrent conditions
Diagnostic testing: dates and test results
Medication use during pregnancy: drug, dates of use, strength, indication
Description of any additional information that might help in interpreting the outcome of the pregnancy
Paediatrician
Name, address, phone number, fax number

LMP = last menstrual period.

Reporting consumers receive a 'thank you' letter that includes the consent form and describes the registry. It also requests the name of her healthcare provider to whom we can send registry information. Once signed, the consent form can later be used to obtain confirmatory medical records of the patient and her offspring for up to 2 years following delivery.

A patient may decline to participate in the Pregnancy Registry at any time. To disenrol, a patient can call the registry manager, whose name and phone number are identified on the consent form. Routine safety department follow-up procedures would then be followed (as required by regulation) but the registry would make no further contact.

The estimated date of delivery (EDD) is calculated for each patient and entered into the NWAES database. At the time of the EDD, an outcome packet is both faxed and mailed to the healthcare provider identified in the report. The packet includes the initial pregnancy questionnaire, prefilled with the information known to date so that it can be confirmed or updated, and an outcome questionnaire requesting information about the outcome of the

pregnancy. If a signed consent is not on file, a blank consent form is again included in this packet.

At least three attempts to obtain information about the outcome of the pregnancy are made within the 3 months following the EDD before the report is considered lost to follow-up. Outcome information is requested repeatedly from the healthcare providers identified in the report by mail, fax and phone. If we are unable to solicit the outcome of the pregnancy from these providers, and if the patient has agreed to participate in the registry by signing a consent form or if the patient contacted the registry herself, the consumer may be contacted for outcome information. The registry will only contact patients who have either contacted the registry themselves or who have signed a consent form.

Pregnancy outcomes are, in most cases, solicited from the mother's obstetric provider. To improve the accuracy of our data and to corroborate outcomes, additional procedures to obtain information on the health status of the infant were initiated in 1999. The outcome questionnaire requests the name of the paediatrician, and paediatric records are requested for all reports with signed informed consent documents to improve the possibility of detecting anomalies that might not have been identified at birth or developmental delays that might subsequently be identified.

While the main focus of the registry is on birth outcomes, information on maternal and neonatal health effects is also solicited and analysed. Specific questions are asked to identify complications during pregnancy, labour and delivery, infections or illnesses during pregnancy, and concurrent medical conditions (table III).

2. Method of Data Analysis

Reports to the registry are classified as prospective or retrospective, according to the information available at the time of the initial report to the company. Prospective reports are those received before the outcome of the pregnancy is known. Retrospective reports are those received after the outcome of the pregnancy is known and include reports made after prenatal testing has identified an abnormality, even if the pregnancy outcome (live birth, termination, spontaneous abortion) has not yet occurred.

Prospective reports are analysed separately from retrospective reports in order to minimise the differential reporting bias inherent in retrospective reporting. Prospective reports provide the numerators and denominators that allow for rate calculations of Pregnancy Registry data while retrospective reports help identify potential AEs that can be evaluated among the prospective cohort.

Rates of pregnancy outcomes in the Pregnancy Registry Program are compared with the rates of pregnancy outcomes in the general US population and, if available, in subpopulations with the relevant disease states. The procedures followed by the Metropolitan Atlanta Congenital Defects Program (MACDP) of the CDC[7] are used to determine whether a reported defect is classified as a congenital anomaly. According to MACDP, major anomalies are included in the rate calculation if they occurred in live born infants or in fetuses >20 weeks' gestation. To be consistent with our comparator rate, anomalies identified in fetuses of <20 weeks' gestation are not included in the rate calculations but are always described in the text and tables of the Pregnancy Registry annual reports. Rates of pregnancy outcomes and birth defects are calculated based on the known outcomes in the prospective cohort, and confidence intervals are calculated to reflect the strength of the finding based on the sample size. Examples of comparator rates, denominators, and references are listed in table IV.

Reports of congenital anomalies are evaluated for timing of exposure (temporality), dose, maternal age and medical history, concomitant medication, biological plausibility, and classification by MACDP criteria. Efforts are made to collect as much information as possible on congenital anomaly reports. Individual anomaly reports are compared with other anomaly reports for similarities in body systems affected, timing of exposure related to embryonic organogenesis and comparison to findings in animal studies. The aggregate rate of anomalies identified in the registry is compared with the US background

Table IV. Prospective reports with known outcomes of pregnancy (from the 2002 annual reports from the Merck pregnancy registries[8,9])

Pregnancy outcomes	No. [registry rate (%)] varicella vaccine	montelukast	Denominator	General US population rates
LBIs	411 (83)[a]	107 (96)[b]	All recognised pregnancies	62%[10]
EABs	33 (7)	2 (2)	All recognised pregnancies	22%[10]
SABs[c]	57 (12)	2 (2)	All spontaneous pregnancy outcomes[d]	10–20%[11]
LFDs[e]	1 (0.2)	0	LBIs plus LFDs	0.7%[12]
Congenital anomalies[f]	8 (1.9) [95% CI 0.8, 3.8][13] g	3 (2.8) [95% CI, 0.6, 8.2][13] h	LBIs plus LFDs	3.2%[14]

a 404 reports, number of live born infants exceeds number of reports due to twins and triplets.

b 106 reports, number of live born infants exceeds number of reports due to twins and triplets.

c Fetal death at <20 weeks gestation.

d Does not include EABs.

e Fetal death at ≥20 weeks gestation (stillbirth).

f Includes only those anomalies present in infants or fetuses of ≥20 weeks' gestation by CDC definition/reference.

g 90% power to detect a 2-fold increased RR compared with the US background rate of congenital anomolies.

h 80% power to detect a 3-fold increased RR compared with the US background rate of congenital anomolies.

CDC = Centers for Disease Control and Prevention (US); **EABs** = elective abortions; **LBIs** = liveborn infants; **LFDs** = late fetal deaths; **RR** = relative risk; **SABs** = spontaneous abortions.

rate. Individual and aggregate reports of congenital anomalies of interest are sent to a consultant teratologist to obtain an objective evaluation of the possible aetiology of the defects.

Data collected in the Pregnancy Registry are analysed on an ongoing basis throughout the year to detect possible signals of birth defects and other negative pregnancy outcomes. An aggregate summary of registry data is included in PSURs that are regularly sent to regulatory agencies.

Annual reports, which are generated for each registry, include rates of pregnancy outcomes in relation to background rates and a list of all congenital anomalies reported, both prospective and retrospective, regardless of causality assessment. This allows for review of the data by the healthcare providers who are making clinical and prescribing decisions. The report, which is available upon request to any US healthcare provider, is sent to each new provider/reporter, and to all healthcare providers who called the registry in the past year. Healthcare providers, including physicians, nurses, pharmacists, genetics counsellors, etc., are then in a better position to counsel their patients. Annual reports are also sent to other interested parties in academia, private practice and government agencies. Staff in the international subsidiaries of Merck & Co., Inc. have access to the annual reports, with which they can formulate responses to inquiries from healthcare providers and consumers in their own countries.

3. A Review of the Issues

The Merck Pregnancy Registry Program was initiated prior to the publication of the FDA Guidelines for Establishing Pregnancy Registries and procedures differ from the guidelines in several areas. Efforts are underway to bring the program into alignment but several issues, including those imposed by the regulatory environment in which the registries are situated, are important to consider. Data from the pregnancy registries for varicella vaccine and for montelukast will be used to illustrate these issues.

3.1 Enrolment

Of 1062 telephone calls to the MNSC regarding exposure to varicella vaccine during pregnancy, 755 (71%) met enrolment criteria and were included in the registry (table V). Most of the exposures occurred when a woman of childbearing potential with a negative history of chickenpox received the im-

Table V. Merck Pregnancy Registry data by product (from the 2002 annual reports from the Merck pregnancy registries[8,9])

Reports	Varicella vaccine		Montelukast	
	no.	%	no.	%
Total eligible[a]	1062		316	
Not enrolled[b]	307	29	97	31
Enrolled	755	71	219	69
Retrospective	38	5	19	9
Prospective	717	95	200	91
Complete	495	69	110	55
Lost to follow-up	148	21	52	26
Pending	74	10	38	19

a Number of reports from US and Puerto Rico (and Canada for varicella vaccine).

b Of those eligible, these did not meet enrolment criteria (or declined enrolment).

munisation prior to the diagnosis of her pregnancy (inadvertent exposure). For montelukast, 219 (69%) of 316 calls to the MNSC met enrolment criteria. Most of these calls were made regarding inadvertent exposure prior to pregnancy diagnosis. However, because of the chronicity of the disease and its potential to compromise the pregnancy,[15] many women continued or reinitiated treatment during the pregnancy (purposeful exposure). Most non-enrolled reports lack either healthcare provider contact information or a patient identifier. Routine WPS&E follow-up procedures are followed when possible, and if information is subsequently received that meets enrolment criteria, the report is then enrolled (for example, a patient may complete a follow-up form providing healthcare provider contact information).

Approximately 70–75% of all initial calls in the registries were from healthcare providers (including physicians, nurses, genetics counsellors and pharmacists); the remainder were from consumers. Reports from consumers and healthcare providers were about equally likely to be completed with outcome of pregnancy information (figure 1).

3.2 Prospective and Retrospective Classifications

More than 90% of calls to the registries were prospective reports made early in pregnancy, before the outcome of the pregnancy was known. In the data collected on varicella vaccine, for example, the number of prospective reports compared with retro-

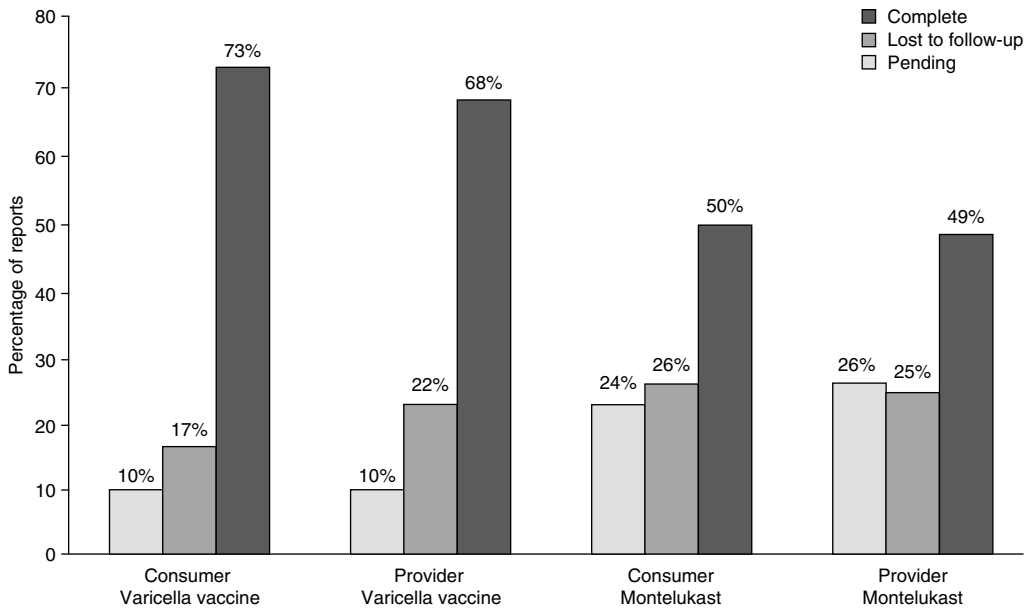

Fig. 1. Merck Pregnancy Registry report completion by initial reporter.

spective reports was 717 to 38, a ratio of 19 : 1 (table V).

Few reports are received concerning patients who have already had prenatal ultrasounds at the time of enrolment (the average gestational week of enrolment in the registries for VARIVAX® and SINGULAIR® was week 9 and week 14, respectively). Reports made after prenatal testing having identified an abnormality are considered retrospective reports (the call was made to the company because of the abnormal finding). Reports with 'normal' prenatal testing results at the time of the initial call are considered prospective based on the following rationale. For those who have had early (first trimester) ultrasounds, the tests were usually performed for pregnancy viability and/or dating purposes. These are unlikely to identify birth defects. Also, even expert ultrasonography is not capable of detecting all anomalies.[16] Therefore, while abnormal findings are usually diagnostic, 'normal' findings may not exclude birth defects. Individual registries may want to consider timing of ultrasound to help determine if reports with 'normal' ultrasound findings should be considered prospective or retrospective.

3.3 Study versus Post-Marketing Environment

The product safety environment differs from the clinical study environment. The Pregnancy Registry is not considered a study *per se*, but is part of an expanded post-marketing surveillance programme. For this reason, institutional review board approval has never been sought for the programme, pregnancy outcomes that are volunteered by callers are accepted in the absence of patient consent, and control groups are not available. If post-marketing reports were to be considered study reports, according to regulations the reporter would have to be asked about the causality of the event. If the reporter stated that the congenital anomaly, for example, was definitely not related to the drug exposure, then, by regulation, the report would not be sent to regulatory agencies. Keeping these reports in the post-marketing environment allows for more regulatory oversight than does classifying them as study reports.

3.4 Consent

It is important to remember that the Pregnancy Registry has little access to the patients themselves, and that in most cases the healthcare provider must obtain the consent, and that most consent forms are never returned. We believe that the informed consent is between the patient and her healthcare provider.

Signed consent was obtained in 23% of enrolled prospective reports for varicella vaccine[2] and in 35% of enrolled prospective reports for montelukast. Most consent forms are not returned (consent unknown; table VI) and few patients actually refused to give consent (seven patients and five patients, respectively). Figure 2 compares the completion of reports in the cohorts with and without consent (complete, pending or lost to follow-up). Figure 3 depicts the pregnancy outcomes in completed reports by consent status. It is important to note that while receipt of informed consent may help to minimise the number of patients lost to follow-up, the reported pregnancy outcomes varied minimally by consent status. The slightly larger number of reported spontaneous abortions in the varicella vaccine cohort with unknown consent compared with the cohort with consent may have resulted from there being fewer patient visits in which to obtain

Table VI. Merck Pregnancy Registry consent by product

Reports	Varicella vaccine[a]		Montelukast	
	no.	%	no.	%
Prospective enrolled	294		200	
Signed consent	69	23	70	35
complete	56	81	58	83
lost to follow-up	3	4	1	1
pending	10	15	11	16
Consent unknown	225	77	130	65
Refused (disenrolled)	7		5	

a VARIVAX® registry started in 1995, consent procedure initiated mid-1998. Number and percentage for varicella vaccine calculated from 1999 to present.

2 VARIVAX® registry started in 1995, consent procedures initiated mid-1998. Rates are calculated from 1999 onwards.

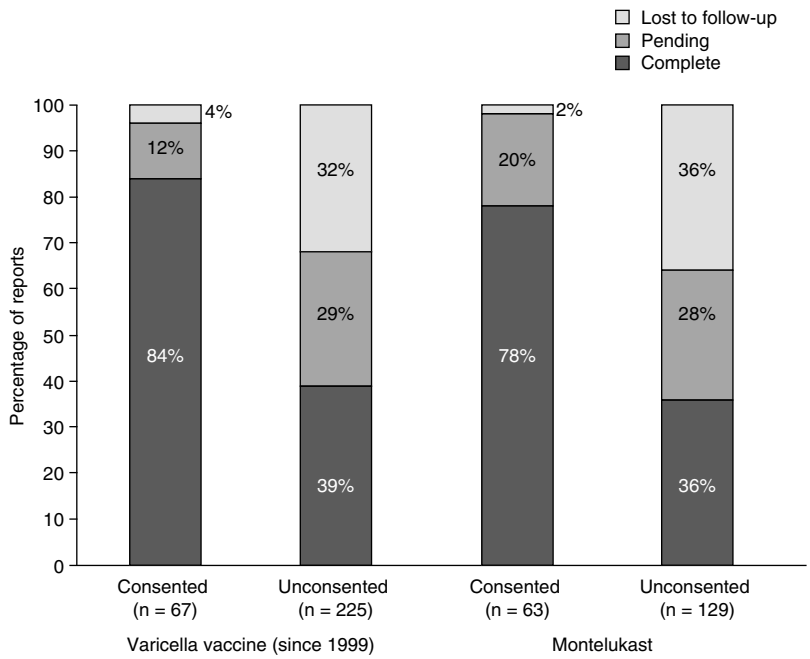

Fig. 2. Outcome status of enrolled prospective reports from Merck Pregnancy Registry: consented vs unconsented cohorts. VARIVAX® registry started in 1995, consent procedures initiated mid-1998. Rates are calculated from 1999 onwards.

consent for patients whose pregnancies ended in miscarriage.

We continually re-evaluate our efforts to improve the return of signed consent forms. Despite our attempts to encourage patient consent and despite our provision of the consent form many times to all patients and healthcare providers who contact the registry, the percentage of patients who have signed consent forms is low. Regardless of the consent status of the patient, healthcare providers and patients continue to spontaneously report outcome of pregnancy information to the company, as they should be encouraged to do. If we did not include the data from patients who have neither given nor refused consent, important information would be kept from healthcare providers and the public. Unlike research studies, post-marketing surveillance of AEs associated with medicinal products has never required written patient consent but is an important public health activity.

In place of the informed consent, anonymous reporting has been suggested as a way of maintaining patient confidentiality, but the need to obtain information on the outcome of pregnancy after an interval of time necessitates the collection of a patient identifier (name, date of birth, initials or medical record number). Patient confidentiality is guarded by the use of the password-protected NWAES database, by the use of patient identifiers only when trying to collect follow-up information from healthcare providers, and by aggregate reporting. Identities of the patients and the healthcare providers are never revealed to any outside sources, except as required by law when submitting reports to regulators.

The risk to the patient is considered minimal.[6] We try to obtain consent because it is preferable to have the patient informed and involved, and it allows follow-up with paediatric staff to confirm the health of the baby. However, requiring consent could limit the ability to find a safety signal that might identify a possible teratogen; thus the importance to the public health overrides the minimal risk to the patient.[17]

4. Health Insurance Portability and Accountability Act

The use of the Pregnancy Registry design by industry has allowed for the collection and analysis of data on the effects of drug exposures on human pregnancies that has otherwise been difficult to obtain. These efforts, however, may be curtailed by the implementation of new privacy regulations in the US (e.g. the Health Insurance Portability and Accountability Act [HIPAA]). Under HIPAA, a covered healthcare provider may disclose health information related to an AE to a pharmaceutical manufacturer without seeking patient authorisation. Section 164.512(b) states: "A covered entity may disclose protected health information for the public health activities and purposes…to…(iii) a person subject to the jurisdiction of the Food and Drug Administration: (A) to collect or report adverse events …".[18] However, it is unclear at this time if healthcare providers are aware of this provision. If healthcare providers become reluctant to share information on exposures during pregnancy with the drug company, we fear that efforts to describe the safety profile of drugs and biologics used during pregnancy will be severely compromised. This may unfortunately result in the delayed recognition of a teratogen, the withholding of treatment from pregnant women who may have benefited from medical intervention, or the termination of wanted pregnancies due to fear of the unknown risk of the exposure.

4.1 Advisory Committee

The CDC Advisory Committee was helpful in the design and evolution of the Pregnancy Registry Program and CDC reviewers and later, an independent consultant teratologist, reviewed individual reports. The FDA guidance recommends an independent data monitoring committee to review data and this suggestion is currently under consideration for implementation.

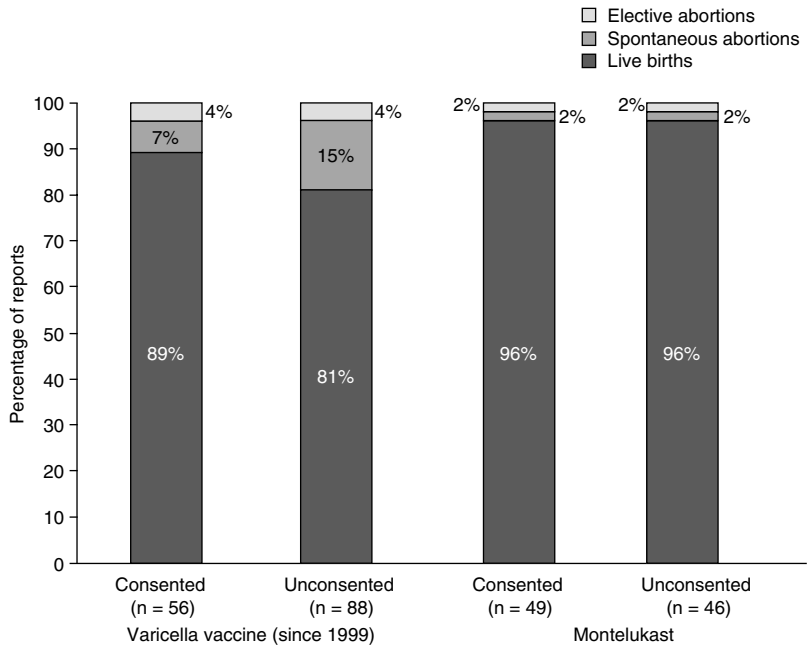

Fig. 3. Pregnancy outcomes of prospective complete reports from Merck Pregnancy Registry: consented vs unconsented cohorts. VARIVAX® registry started in 1995, consent procedures initiated mid-1998. Rates are calculated from 1999 onwards.

4.2 Comparison Groups

The calculation of outcome rates is performed in the same manner as was done by the authors of our reference rates in order for the results to be comparable. Outcomes of pregnancies reported to the pregnancy registries to date have been similar to the expected background rates in the general US population (table IV). Rates of congenital anomalies have not been statistically different from the background rates and no cluster of related anomalies have been identified. Healthcare professionals should refer to the product-specific annual reports for detailed information.[8,9,19-21]

The FDA guidance document on pregnancy registries recommends the collection of data on a control group with characteristics similar to the patient population, but they recognise that this may not be possible to do.[6] Post-marketing surveillance including the Pregnancy Registry Program, relies upon spontaneous reporting to identify cases. Women who are not exposed to Merck products do not make spontaneous calls to the registry. Collecting information on consumers who have not used our products is inappropriate, as would be the case if we asked healthcare providers to give us a second, unexposed patient as a control. For these reasons, we compare the outcomes of pregnancies in the registry with the published US population figures that are generally accepted as standards. We also review literature reports that describe pregnancy outcomes in populations of interest, such as patients with asthma or migraine (see annual reports[9,19] for details). The CDC MACDP rate is the comparator group as it was considered important to use a widely respected and accepted source for comparison of data. Limitations of this surveillance system are discussed in the MACDP procedure manual[7] and include exclusion of defects with diagnoses after 6 years of age, exclusion of defects in fetuses of <20 weeks gestation, and omission of births occurring outside of hospitals and in hospitals outside of the catchment area.

4.3 Confirming Outcomes

Although gross abnormalities are readily identified at the time of delivery, more subtle or internal anomalies may not be detected until the paediatric newborn examination, or even later. We have addressed that concern by implementing the request for paediatric medical records to corroborate outcomes and to detect any previously unidentified anomalies. No major anomalies have been identified through record review and this has increased our confidence in the veracity of the outcome data collected. However, we have picked up some miscellaneous anomalies in reviews of paediatric records including a dacryostenosis (stenosis of nasolacrimal duct), and a valgus foot deviation ('softly deviated, returns to midline easily') following montelukast exposure, and an eyelid ptosis ('mild palpebral fissure asymmetry'), and a possible hearing impairment following varicella vaccine exposure. However, we can only obtain medical records on those participants who have signed consent, which limits the data available for review.

4.4 Pregnancy Losses

We suspect that there is under-reporting of elective and spontaneous abortions both for privacy reasons and because these outcomes may occur before an exposed pregnancy might be reported to the registry. The background rate of spontaneous abortions in the US population is 10–20% of recognised pregnancies.[11] Table IV indicates that the reported rate for varicella vaccine (12%) was within the expected population rate, while the rate for montelukast (2%) was well below the expected population rate. Eighty-two percent of varicella vaccine reports were received prior to 12 weeks gestation compared with 52% for montelukast (as stated in section 3.2, the average week of gestation at time of initial report for varicella vaccine was 9 and for montelukast 14). For varicella vaccine, more reports were made to the registry prior to the time when a spontaneous abortion is most likely to occur. For montelukast, spontaneous abortions may have occurred prior to the time when a report would be made to the registry, possibly resulting in fewer

reports of spontaneous abortion. For both groups, women planning an elective abortion may be unlikely to contact the registry.

4.5 Lost to Follow-Up

Because all reports of exposure during pregnancy are, by regulation, collected by the company, determination of enrolment in the Merck Pregnancy Registry Program is based on information given in the initial report, not on the agreement of the patient or the healthcare provider to participate. Therefore, lost to follow-up rates are high (21% for varicella vaccine and 26% for montelukast). However, if only patients who have signed a consent form were considered enrolled, lost to follow-up rates would be much lower (4% for varicella vaccine and 1% for montelukast). The high lost to follow-up rates are due to the liberal enrolment criteria and our commitment to consider as 'enrolled' all reports that provide enough information for us to perform follow-up.

Reports are 'lost to follow-up' for a variety of reasons. In the time interval between the initial report and the pregnancy outcome, patients may move or change healthcare providers. In some cases, the healthcare provider who reported the exposure is not the patient's obstetric care provider and thus, may not be aware of the outcome of the pregnancy in a timely manner. Immunologists, pharmacists, allergists, genetics counsellors and other specialists make initial reports to the Pregnancy Registry but may not continue a relationship with the patient to have access to pregnancy outcome information. Names of alternative healthcare providers to contact are requested on the questionnaires (table II and table III).

4.6 International Reporting

Enrolment is presently restricted to women in the US in order to limit reports that are lost to follow-up. However, all international reports and all non-enrolled US reports of exposure during pregnancy are entered into the NWAES database and are reviewed by the registry staff, with special attention paid to any reports of congenital anomalies. Anomalies of interest, even when not in the enrolled cohort, are described in the annual reports.

4.7 Advantages of the Registry Design

In addition to the registry's ability to detect a signal regarding teratogenicity, other issues of medical significance may be identified using registry data. For example, a series of medication errors was discovered by the registry wherein orders for varicella zoster immunoglobulin were misinterpreted to be orders for varicella zoster immunisation and varicella vaccine was erroneously administered to pregnant patients who had been exposed to chickenpox. This information has been published to alert the healthcare community of the potential for medication error.[22,23]

Industry-run pregnancy registries are required to forward exposure during pregnancy information to the FDA and other worldwide regulatory agencies. Also, information on aggregate data is shared with the reporters and other healthcare providers as it is gathered, not at the end of the study. By design, industry-run Pregnancy Registry data have regulatory oversight and monitoring, and healthcare providers can use the information to inform their practice on an ongoing basis.

4.8 Limitations and Strengths

The limitations of post-marketing surveillance are well known. Reliance upon the voluntary reporting of individuals and healthcare professionals is known to be subject to various types of bias including under-reporting and selective reporting caused by self-selection, mass-media coverage, etc.[24,25] Retrospective reports are more likely to contain abnormal outcomes and unusual cases, and are less likely to be representative of the general population than are prospective reports. The over-reporting of abnormal outcomes may also occur in prospective reports, as healthcare providers may be more inclined to report unusual outcomes whereas normal outcomes may not be reported and thus be lost to follow-up.

Small sample size is a major limitation. The collection and follow-up of exposure during preg-

nancy reports is a slow, time-consuming, personnel-intensive process. It can take years before a registry can amass a cohort large enough to achieve statistical significance. Because of the small numbers of patients enrolled, and the small number of congenital anomalies reported, the confidence intervals around the rates are wide. While it can be reassuring to find rates of anomalies similar to the background population, one must be cautious in interpreting the significance of the findings with such low numbers. It would be difficult for a registry to identify an increase in the rate of individual and rare defects.

The strength of the registry design lies in its ability to gather pregnancy outcome reports early in the life of a product and to recognise and analyse unusual birth defects or patterns of defects with timing of exposure and biological plausibility considerations.

5. Conclusion

For pregnant women, it is important that the risk of the medication be weighed against the risk of the disease for which treatment is being considered. Women who discover they are pregnant after exposure to a drug and pregnant women who have a condition that requires continued treatment during pregnancy are told to balance the benefits and risks of the exposure to justify continuation of treatment, discontinuation of treatment, or, possibly, pregnancy termination. It is difficult for these women and their healthcare providers to perform this analysis if there is little information available on human exposure.

The FDA's Pregnancy Labeling Taskforce has proposed changes to the pregnancy section of the product circulars[26,27] that will allow the label to be updated with human exposure information as it becomes available. Similar discussions have taken place among regulators in Europe. It is important that such information be available for evaluation and incorporation into the product circular to enable pregnant women and their healthcare providers to decide if the potential benefit to the mother and the baby justifies the potential risk to the fetus. Our data show that pregnancy registries can be used to review human exposure data in a systematic fashion so that useful information can be shared with healthcare providers and their patients.

Pregnancy registry programmes, run by the pharmaceutical industry, provide one means of collecting human exposure data that are otherwise difficult to obtain. The registry's strength lies in its potential to detect signals of possible toxicity early in the life of a product. These signals may identify issues that would need to be explored in more formal epidemiological studies using other means of data collection, such as health maintenance organisation and pharmacy-benefit databases, national reporting systems, teratogen information services and case control studies. To help pregnant women and their healthcare providers gain access to information to inform decision making at this critical time of life, all feasible methods of data collection should be encouraged. A cooperative spirit of data collection, information sharing and dissemination of findings should exist.

Readers are encouraged to prospectively report exposed pregnancies as early in pregnancy as possible to current pregnancy registries (see table I) or to the relevant drug company. To request a product-specific annual report or to report an exposure during pregnancy to a Merck registry product, please call the Merck Pregnancy Registry Program at 800-986-8999 or go to the website at www.merckpregnancyregistries.com.

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