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Approach to evaluating pregnancy safety of anti-rheumatic medications in the OTIS MotherToBaby pregnancy studies: what have we learned?

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Abstract

For the last 30 years, pregnancy exposure studies, with varying methodologies, have been the mainstay of post-marketing surveillance for new drugs likely to be used by women of reproductive age. While they provide valuable data to inform use during pregnancy, they have limitations that render them necessary but not sufficient in supplying timely information to patients and prescribers. The Organization of Teratology Information Specialists MotherToBaby Pregnancy Studies' collaborative research group operates to help fill this gap. This paper provides an overview of the research that has been and is currently being conducted, as well as best practices determined over the past two decades. The Organization of Teratology Information Specialists MotherToBaby studies can provide earlier signaling with regard to concerns following possible teratogenic exposures, which when examined in conjunction with larger database studies and case-control designs, can move us closer to developing a fuller picture of drug safety for women of reproductive age.

Key words: autoinflammatory conditions, rheumatoid arthritis, pregnancy and rheumatic disease, biological therapies, study design

REVIEW

Rheumatology key messages

- Pregnancy exposure registries are the main source of early information of medication safety.
- MotherToBaby studies have the advantage of an internal comparison group and maternal disease severity data.
- Challenges in MotherToBaby studies are recruitment rate, sample size and representativeness of the sample.

Introduction

Dating back to 1984 with the initiation of the Acyclovir Pregnancy Registry [1] (see Table 1), one approach to evaluating the safety of medications and vaccines in pregnancy with respect to fetal and maternal outcomes has been the pregnancy registry. For the last 30 years, these pregnancy exposure studies, with varying methodologies, have been the mainstay of post-marketing surveillance for new drugs likely to be used by women of reproductive age. The number of studies has increased over time; currently, the US Food and Drug Administration (FDA) website contains 107 entries for pregnancy exposure studies [2].

Pregnancy exposure studies are considered a useful tool for monitoring for safety signals for new and often infrequently used products in pregnancy. However, one limitation of these studies is that they are typically statistically underpowered; and may only detect strong associations between exposure and rare outcomes such as major birth defects. A further concern has been that many pregnancy exposure studies have no internal comparison group, and therefore are limited to making external comparisons to the general population [3]. In addition, enrolment rates in these registries have been challenging and have led to long waits for final results before a pregnancy exposure study is formally closed [4]. Examples are a 15-year term for the acyclovir registry [1], 11 years for the bupropion registry [5], 17 years for the varicella vaccine registry [6] and ~12 years expected for completion of the omalizumab pregnancy exposure study [7].

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Table 1 Prospective registry of acyclovir use in pregnancy, outcomes by trimester

Earliest trimester of exposure	Outcomes with birth defects	Outcomes without birth defects[a]			Total, *n* (%)
		Live births without birth defects	Spontaneous pregnancy losses	Induced abortions	
Unspecified	0	1	0	1	2
First	19	577[b]	77	83	756 (61)
Second	2	194[c]	0	1	197 (16)
Third	7	282[d]	2	0	291 (23)
Total	28	1054	79	85	1246 (100)

Adapted from Stone *et al.* Pregnancy outcomes following systemic prenatal acyclovir exposure: Conclusions from the international acyclovir pregnancy registry registry, 1984-1999. Birth Def Res A Clin Mol Teratol 70:201–7. Copyright © 2004 by John Wiley Sons, Inc. Adapted with permission of John Wiley & Sons, Inc. This table excludes patients with exposure to topical acyclovir only. [a]Birth defect not reported but cannot be ruled out. [b]Includes seven sets of twins. [c]Includes two sets of twins. [d]Includes three sets of twins.

In May of 2014, the FDA hosted a public meeting focused on the utility of pregnancy registries as a method for evaluating the safety of new medications and vaccines given the known limitations [8]. The panel reviewed the above-stated concerns regarding the effectiveness and efficiency of pregnancy registries, as well as some alternative approaches. These included study designs with an internal comparator group, and disease-based studies instead of single-drug registries, such as the North American Antiepileptic Drugs in Pregnancy Registry [9]. Complementary designs such as linked mother-baby claims databases, for example, the FDA-funded Medication in Pregnancy Risk Evaluation Program [10, 11], and registries combined with case-control studies, for example, Vaccines and Medications in Pregnancy Safety Surveillance programme, were also reviewed [12]. The general conclusions of the participants were that pregnancy exposure studies may be necessary but are not sufficient to obtain the needed information in a timely manner.

OTIS MotherToBaby pregnancy studies

The Organization of Teratology Information Specialists (OTIS) is a non-profit organization made up of a network of 15 MotherToBaby services located throughout the USA and Canada that provide expert counselling and information regarding fetal and infant exposures to pregnant and breastfeeding women and their health care providers (www.mothertobaby.org). To address the need for more evidence-based information to support this counselling, in 1998, OTIS established a collaborative research group to study pregnancy outcomes following selected exposures (http://mothertobaby.org/pregnancy-studies).

A major focus of these studies has been autoimmune/autoinflammatory diseases and their treatments, in part due to the number of new medications being marketed in these therapeutic areas, as well as the frequent predominance of many of these diseases among women of reproductive age.

Study design

The design of these studies is built around a core model that contains the following components: a prospective cohort study design with a medication-exposed group, a disease-matched comparison group and a healthy non-diseased comparison group recruited; recruitment of pregnant women in all three cohorts at <20 weeks' gestation followed by three to four maternal telephone interviews, and release of medical records; data collection on demographics, pregnancy and health history, all maternal medication, vaccines, dietary supplements, herbal products, substances used in pregnancy by dose and gestational timing, comorbidities, infections and prenatal tests; one or more maternal self-reported measures of disease severity/symptom control/activity in the exposed and disease-matched cohorts; a specialized and blinded physical examination of live born infants in all three cohorts conducted by one of a team of study pediatricians who evaluate the child for minor and major birth defects, specifically for a pattern of minor anomalies, and capture infant photographs; follow-up for live born infants for a minimum of 1 year postpartum for growth, newly identified congenital malformations and other infant health events such as hospitalizations, serious infections or malignancies.

Women in all three cohorts are recruited through referrals from MotherToBaby sites from spontaneous callers with questions about a wide variety of pregnancy exposures, from obstetric and specialty health care providers, from pharmaceutical companies and from direct to consumer marketing including social media.

It is important to note that there exist no objective parameters to assess disease severity and activity, and that medical records collected for verification of maternal report will not necessarily reveal a match between physician's and patient's perspectives on disease activity and severity. However, collection of this data is deemed critical to determine its effect, if any, on the pregnancy.

In some of the MotherToBaby studies, longer term follow-up includes neurodevelopmental screening and

Table 2 Status of MotherToBaby/OTIS Pregnancy Studies for Rheumatic Disease Medications

Medication	Target sample sizes or final recruitment cohorts 1; 2; 3	Start date–end date	Study status
Leflunomide	Final: 64; 108; 78	1999–2009	Completed Final manuscripts published
Adalimumab	Final: 257; 120; 225	2004–2014	Completed Final manuscript in progress
Etanercept	Final: 370; 164; 296	2005–2012	Completed Final manuscript in progress
Abatacept	Target: 100; 100; 100	2006–	Open for enrollment
Tocilizumab	Target: 100; 100; 100	2010–	Open for enrollment
Certolizumab pegol	Target: 100; 100; 100	2012–	Open for enrollment
Tofacitinib	Target: 100; 100; 100	2013–	Open for enrollment
Ustekinumab	Target: 100	2013–	Open for enrollment
Apremilast	Target: 100; 100; 100	2014–	Open for enrollment

neurodevelopmental testing of the child and mother at late preschool/early school age. Additional measures of maternal stress, depression and anxiety have been incorporated in more recent study years, and mothers who are breastfeeding their infants are offered participation in a breastmilk repository to which they provide samples for future research purposes. Mothers who participate in the breastfeeding follow-up also complete questionnaires regarding infant adverse events.

Sample size

Sample sizes have been estimated at each study outset, and are typically targeted for an *n* of 100 in each cohort. These sample sizes are insufficient to rule out low or moderate risks for major birth defects. However, the inclusion of the physical examination for a pattern of minor anomalies has the advantage of potentially identifying the existence of a characteristic cluster of minor defects that is on the order of what is seen with more moderate level teratogens such as carbamazepine or coumadin. Most MotherToBaby studies, in addition to the three cohorts, also have open-ended recruitment of pregnant women with exposure to the drug of interest who did not meet the cohort enrolment criteria, for example, retrospectively reported cases, off-label indications or enrolment with a second pregnancy. Pregnancies enrolled in these exposure series have similar data collected, and can be an important source of information regarding any consistent patterns of defects or other concerns should they be identified. However, there is no comparison group for exposure series pregnancies, and therefore, the data are descriptive only.

Infrastructure

The MotherToBaby collaborative research group conducts all studies at one dedicated research center located at the University of California San Diego. A permanent team of research and support staff allow for efficiencies across studies. The staff includes study managers, a screening team, an interview team, medical records abstractors, data and quality assurance managers, a pool of statisticians, a marketing team, programmers, psychometrists and a psychologist, an ethics analyst and information technology/security analyst as well as administrative support.

Scientific Advisory Board members for each study have been identified and often fulfill that role for multiple MotherToBaby studies as they have the necessary specific expertise and familiarity with the MotherToBaby study designs.

A set of standard operating procedure manuals has been developed to support all studies. Data collection is currently performed using paper-based interview guides, and these data as well as data abstracted from medical records and examination forms are entered into a custom database housed within the University Health Sciences domain. On-site space is available for storage of paper-based records under secure conditions. Records are ultimately transitioned to electronic form through scanning, and are housed indefinitely.

OTIS MotherToBaby studies of medications for rheumatic diseases

As shown in Table 2, a variety of studies on older and new medications for the treatment of RA, AS and PsA have been completed or are currently under study by OTIS MotherToBaby. The projected sample sizes, start dates and current status are shown for each study. Recruitment rates vary greatly by study, in part due to the prevalence of the disease indication in women of reproductive age, and the frequency of the use of the specific medication. Target recruitment rates in each cohort have not been met in some cases, and in others, they have been exceeded. As has been typical of previous pregnancy registry studies, the three completed registries have taken ~10 years to finalize. An example of the outcomes reported in each of the three registries completed

Table 3 Major and minor structural anomalies in infants of women in the LEF-treated and comparison groups

Anomaly	LEF group	Disease-matched comparison group	Healthy comparison group
Major structural defects in live births, *n* (%) and diagnoses	3/56 (5.4)	4/95 (4.2)[a]	3/72 (4.2)[b,c]
Major structural defects in pregnancy losses, *n* (%) and diagnoses	0/7	3/11 (27.3)	0/3
Major structural defects in all pregnancies, *n* (%)[d]	3/63 (4.8)	7/106 (6.6)	3/75 (4.0)
Functional problems, diagnoses	1 hydronephrosis grade 2; 1 bilateral vesicoureteral reflux	1 unilateral hydronephrosis; 1 vesicoureteral reflux with unilateral duplicated collecting system	1 congenital esotropia; 1 neonatal encephalopathy and seizures secondary to subarachnoid bleed; 1 tracheomalacia
Minor structural anomalies, n (%)[e]			
0–1	12/51 (23.5)	39/90 (43.3)	33/65 (50.8)
2	15/51 (29.4)	22/90 (24.4)	13/65 (20.0)
⩾3	24/51 (47.1)	29/90 (32.2)	19/65 (29.2)
Pattern of minor anomalies	0	0	0

Adapted from Chambers *et al.* Birth outcomes in women who have taken leflunomide during pregnancy. Arthritis Rheumatol 62:1494–503. Copyright © 2010 by John Wiley Sons, Inc. Adapted with permission from John Wiley & Sons, Inc. One twin of each liveborn twin pair was randomly selected for analysis; however, no twin was malformed. [a]Reported by mother. [b]Reported by mother; inguinal hernia in a full-term infant, requiring surgery. [c]Persistent and not due to trauma. [d]All pregnancies excluding loss to follow-up. [e]$P = 0.05$ for three-group overall comparison; $P = 0.10$ for three-group comparison of infants with three or more minor structural anomalies, by Chi-square test.

using this design to study leflunomide is shown in Tables 3 and 4 [13, 14].

Lessons learned

Challenges in recruitment

As described in the Introduction, there have been challenges in completing the OTIS MotherToBaby pregnancy cohort studies as quickly as originally planned. In some cases, this is likely due to the reality of infrequent use of the specific medication in women who become pregnant. In those situations, often even an extended period of time would not be sufficient to recruit the original sample projected. Nevertheless, the series of exposed pregnancies can be carefully described in a publication and viewed in the context of other data in the literature.

Another barrier to recruitment is lack of awareness that the OTIS MotherToBaby study exists. Marketing efforts that are directed to the consumer have been somewhat successful but primarily for identifying participants eligible for the two comparison groups. The primary pathway to recruitment for a woman with exposure to a new drug is the health care provider, and to the extent that the provider is not aware of the study, or does not facilitate their patient's referral, there are missed opportunities. To encourage provider referrals, OTIS MotherToBaby regularly communicates with health care professionals through exhibits at professional society conferences and other venues.

Other sources of recruitment are through the pharmaceutical company; efforts are made to educate their field teams to raise awareness, to encourage facilitated referrals of pregnant women from safety or medical information groups, and referrals of incidental pregnancies that occur in post marketing safety studies.

Finally, even among women who do come in contact with the study, some will decline to enrol. The most common reasons given are lack of time and unwillingness to release medical records. In response to the former, OTIS MotherToBaby interviewers provide flexibility to the potential participant in when and how they complete the interviews. For some data collection measures, completion is offered online at the participant's convenience.

Retention of participants

One feature of OTIS MotherToBaby studies is that the enrolled participant is always the pregnant woman. She is engaged in the study from the start and has relatively frequent contact with study staff. This relationship, as well as the offer of the specialized physical exam and in some cases neurodevelopmental follow-up for the child, is thought to enhance retention. In past studies, across all three cohorts, lost-to-follow-up rates in OTIS MotherToBaby pregnancy studies have typically been $<5\%$.

However, with the increased emphasis on new and promising marketing efforts such as social media, there is concern that these exceptionally low lost-to-follow-up rates will erode. The OTIS MotherToBaby study team has had some limited experience with offering gift cards or other incentives to study participants, tied to each completed study-related data collection event. In addition to being costly, there has been some concern that an incentive-based motivation for participation (rather than

Table 4 Pregnancy outcomes of participants in LEF registry

Characteristic	LEF group ($n = 64$)	Disease-matched comparison group ($n = 108$)	Healthy comparison group ($n = 78$)
Liveborn infant	56 (87.5)	95 (88.0)	72 (92.3)
Spontaneous abortion	5 (7.8)	8 (7.4)	3 (3.9)
Stillbirth	0	1 (0.9)	0
Blighted ovum	1 (1.6)	0	0
Elective termination	1 (1.6)	2 (1.9)	0
Lost to follow-up	1 (1.6)	2 (1.9)	3 (3.8)

Adapted from Chambers CD *et al.* Birth outcomes in women who have taken leflunomide during pregnancy. Arthritis Rheum 62:1494–503. Copyright © 2010 by John Wiley Sons, Inc. Adapted with permission from John Wiley & Sons, Inc.

altruism) will threaten retention rates; however, a full evaluation of the effect of incentives has not yet been performed.

Representativeness of the sample

Typical of observational studies that depend on volunteers, there is a bias in women who tend to enroll in OTIS MotherToBaby studies towards higher education level/higher socioeconomic status and less diversity in race/ethnicity than in the general population; this is true across all three cohorts, and not entirely due to differential access to new medications. OTIS MotherToBaby studies have initiated efforts to address this by adding recruitment sites at prenatal clinics and other locations that serve diverse populations. However, this is not expected to influence the diversity of women with exposure to the target medications, where referrals from specialty clinicians are heavily relied upon. While this bias is not thought to pose a threat to the internal validity of the studies, as internal comparison group women are also enrolled, a better understanding of any differences in baseline risks across more diverse populations would be ideal.

Opportunities for additional research using MotherToBaby studies

Although OTIS MotherToBaby studies are each focused on addressing hypotheses related to a specific drug, and not designed as one disease-based registry, the pooled data across studies have proven to be very useful for addressing these ancillary questions. For example, data on prenatal exposure to MTX that was collected across multiple OTIS MotherToBaby studies was able to be combined with data from multiple European countries with teratogen services similar to MotherToBaby to produce an analysis of birth outcomes in a relatively large sample [15]. Data from OTIS MotherToBaby studies have also been used to examine the value of maternally reported disease severity/activity measures in predicting preterm delivery, reduced birth weight or delivery by caesarean section [16]. Finally, various trainees, rheumatology fellows and visiting scholars have been able to produce valuable analyses on a variety of different topics. These have included an analysis of the frequency of use of NSAIDs in the third trimester and birth outcomes [17], an analysis and review of the incidence and size of infantile hemangiomas in women with rheumatic and other inflammatory diseases [18], a review of the data on safety of corticosteroid use in pregnancy [19], and an analysis of trajectories of prednisone use across gestation as these relate to preterm delivery [20].

The future of MotherToBaby studies

While Margulis and Andrews [21] recently proposed that claims or other database studies can now effectively replace pregnancy registries, that time has not yet come. The advantages of database studies that do not require consent for participation are many, yet they still are lacking in ability to address multiple confounding exposures or factors including shared medications, drugs that are not taken as prescribed, over-the-counter medication use, substance use and folic acid supplementation. With respect to sample sizes, the limited number of exposed pregnancies that occur for a given drug is a challenge for some medications no matter how many millions of individual patients are included in the database. OTIS MotherToBaby studies, with their known limitations, can provide early (or earlier) information on pregnancy outcomes. Additional opportunities that could enhance the value and efficiency of these studies would be the routine incorporation of data on pregnancy outcomes following paternal exposures, and expanded collaboration with similar projects in countries outside of North America including the European Network of Teratology Information Services, with the specialized features of the OTIS MotherToBaby study design including the infant physical examination, as well as attention to control for the maternal underlying disease, this type of approach can still complement others, including database and case-control designs, as well as pharmacovigilance data. With the revision of the Pregnancy and Lactation Labelling Rule now in the implementation phase, the lack of sufficient human pregnancy safety data for most drugs on the market in the USA today will become more apparent to clinicians (and their patients). This highlights the need for a systematic and continuous flow of

resources devoted to developing this critical information more efficiently but also with a high degree of rigor.

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