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PROSPECTIVE FOLLOW-UP OF INFANTS EXPOSED TO 5-AMINOSALICYLIC ACID CONTAINING DRUGS THROUGH MATERNAL MILK

by

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A thesis submitted in conformity with the requirements
for the degree of Master of Science
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ABSTRACT

The aim of this prospective cohort study was to estimate the risk of the adverse effects in infants breastfed by mothers receiving 5-ASA-containing drugs while lactating. We conducted telephone interviews with 121 women exposed to the drugs while lactating and 121 controls. The mean age for the exposed infants at the time of follow-up was 22 ± 20 months while the mean age for the non-exposed infants at the time of follow-up was 21 ± 18 months. Most of the exposed group had been taking the medication long term at least throughout the pregnancy. Based on maternal reports there were 14 (12%) clinical events in the infants of the exposed group and 13 (11%) in the control group (p=0.4). The profile of clinical events in the infants were similar in the two groups and often were explained by other causes. The results of this study suggest that 5-ASA-containing compounds do not pose a significant risk to breastfed infants.

ACKNOWLEDGEMENTS

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Myla E. Moretti

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LIST OF ABBREVIATIONS

5-ASA	5-Aminosalicylic Acid
AAP	American Academy of Pediatrics
ANOVA	Analysis of Variance
CI	Confidence Intervals
SD	Standard Deviation
SIDS	Sudden Infant Death Syndrome

1. INTRODUCTION

1.1 Purpose of the Study

The MotheRisk program in Toronto, which is a specialized counselling program for pregnant and lactating women, counsels patients who express concern about exposure to medications while breastfeeding. These concerns pertain to fear of causing untoward effects in the infant. Breastfeeding mothers generally wish to avoid drug therapy whenever possible in order to circumvent these difficulties[1]. However, for chronic diseases that would result in significant compromise of maternal health without treatment, avoiding therapy is simply not a possibility. Inflammatory bowel disease and its treatment, 5-aminosalicylic acid (5-ASA), is an example of this. Adequate counselling supported by sufficient human data on the safety of a particular agent are required to alleviate the fears of mothers and protect the health of the nursing infant.

Despite the relatively low concentrations in milk, the use of 5-ASA-containing drugs in a lactating patient has been a matter of concern. The concerns arise from case reports of adverse reactions in infants whose mothers were taking 5-ASA or sulfasalazine[2,3]. Consequently, the American Academy of Pediatrics recommends that these drugs be given to breastfeeding mothers with caution[4]. Given the relatively common use of 5-ASA-containing drugs in women in their childbearing years,[5,6] it is likely that these reported observations of adverse events represent the most severe end of the spectrum.

1.2 Hypothesis:

It is my hypothesis that the incidence of adverse reactions in breastfed infants exposed to 5-ASA-containing drugs through milk is very low and that severe reactions such as those reported in the literature are rare. Most women are able to breastfeed safely.

1.3 Objectives:

By following a group of women taking 5-ASA-containing drugs during lactation it is my objective to determine the incidence of adverse reactions in their breastfed infants. As well, I will aim to determine more specifically whether the incidence of diarrhea is an increased risk for these infants. These objectives will allow for a better risk assessment for patients and health care providers faced with this clinical scenario in the future.

1.4 Background: Breastfeeding

It is clear that breastfeeding is the superior form of infant nutrition, providing benefits that are visible across all cultural, environmental, and geographic barriers[7]. Although the advantages are quite striking in underdeveloped and developing nations, the benefits are present even in developed nations such as Canada[8]. Exclusive breastfeeding is associated with significant health benefits to the child. These include reductions in many newborn illnesses such as otitis media,[9] SIDS,[10,11] viral diarrhea,[12] necrotising enterocolitis,[13,14] and decreased morbidity from respiratory syncytial virus infections[15,16]. Moreover, several investigators have recently shown that breast milk may have benefits on the neurodevelopment of the child[17,18,19,20]. Because of these obvious benefits the Canadian Pediatric Society[8]

and the American Academy of Pediatrics[7], have recommended that exclusive breastfeeding be encouraged in almost all clinical settings and should continue for at least the first year of life or longer[7,8]. This is further supported by various initiatives, including the "Baby-Friendly" hospital by the World Health Organization,[21] which fully support the notion that breast milk is nutritionally and immunologically the best food source for infants.

It appears that for many years now, the general public in industrialized nations have not widely accepted these clear benefits or have succumbed to the influences of society and the media. This is evidenced as we look at historical trends. With the advent of artificial infant formulas in the 1950s and throughout the 1970s, breastfeeding rates declined significantly,[22,23] and it became less socially acceptable to breastfeed[24]. As the general public, and more importantly, childbearing women become aware and educated about both the advantages of breastfeeding and its advocation by major medical bodies, the rate of breastfeeding can be expected to increase once again,

Although, under ideal situations, the vast majority of women are capable of breastfeeding, for many reasons they either do not initiate breastfeeding or discontinue breastfeeding prematurely. Some of the reasons can be attributed to the perception that they have insufficient milk,[25,26] pain, or discomfort with breastfeeding,[26] embarrassment or inconvenience,[26] infant illness or abnormality[27,28] and anatomical difficulties[29] (various anomalies may make breastfeeding extremely difficult). Recently, however, we have shown that maternal illness and maternal drug exposure are extremely important indicators of failure to initiate or continue breastfeeding[30].

1.5 Drug Transport into Human Milk

Almost all drugs will gain access to the milk. This is theoretically obvious when we consider the physicochemical properties of drugs and the biological properties of breast milk as with any other body fluid or tissue. In general, when measurements have been performed in humans, almost all drugs have been detected. Since most drugs are believed to diffuse into breast milk, transport across the mammary barrier is governed by standard pharmacokinetic and pharmacodynamic principles. The properties which dictate the amount of diffusion of a drug into breast milk are: the lipid solubility of the drug, the protein-binding of the drug, its acid/base characteristics, molecular weight, maternal systemic bioavailability and its half life[31]. To further identify the amount of drug that the infant will be systemically exposed to one must also consider the gastrointestinal absorption or oral bioavailability[32] and the metabolism, elimination, and half-life of the drug in infants[33].

Human milk can be considered a compartment just as any other tissue. The reason most drugs gain access into milk is generally due to several common features. That is, they are frequently all small in molecular weight, usually less than 100-200 Da[34] and they are frequently weak acids or bases[35]. Their small molecular weight allows for easy diffusion across the lipid bilayers of the mammary epithelia (alveolar cells) into mature milk. Although, in the early stages of lactation, there are gaps between alveolar cells of the mammary glands which excrete milk[31] and molecules may have easier access across these cell gaps. Since human milk is also slightly more acidic than blood (7.2 vs 7.4)[36], basic molecules will tend to become ionized, depending on their pKa and become "ion trapped" in the milk. Breast milk is relatively high in fat, about 3-4%[37], such that drugs which are highly lipid-soluble will tend to diffuse into breast milk to a greater extent than drugs which are not lipophilic. The protein binding of a drug also influences the diffusion into breast milk since it is only free

drug that is able to diffuse across the lipid bilayer. So, highly bound drugs are less likely to diffuse into human milk.

The mother's plasma concentration of a drug will also influence the amount of drug in milk. This is because the concentrations in milk tend to correlate with concentrations in maternal plasma[38] and the two follow similar concentration-time profiles. In fact, when sampled over time, the concentration of drug in milk will display an initial peak followed by a more gradual decline in concentration. I have shown this previously with ketoconazole (a systemic antifungal agent)[39]. Maternal breast milk samples were taken over 12 hours after the drug had reached steady state in the mother. The area under the concentration-time curve is then used to estimate infant exposure. As the maternal plasma concentrations of a drug fall, so will the drug concentrations in breast milk although there will be a lag in the breast milk concentrations to allow for distribution. Maternal plasma half life of a particular drug will also influence the amount of drug in milk because of this feature. Drugs with very short half life may only be present in the maternal systemic circulation for brief periods. They may peak rapidly in plasma and dissipate just as rapidly, which may not allow for significant transfer into milk.

1.5.1 What is the M:P ratio?

The milk to maternal plasma concentration ratio (M:P) is just that, an expression to represent the amount of drug reaching milk relative to maternal plasma concentrations. Although the M:P ratio may fluctuate somewhat, most drugs will display a relatively constant value[31,38], stabilizing once the drug has achieved steady state concentrations in the mother's plasma and hence the milk. We may also see interindividual fluctuations which may reflect why some infants will display adverse reactions, whereas others will not.

Once a drug has entered into the breast milk compartment, estimating the exposure to the infant must still consider the disposition of the drug in the infant. That is, even if the drug is ingested by the infant, oral bioavailability and half-life in the infant play important roles in determining systemic exposure by the infant. Many drugs which enter the infant's gastrointestinal tract become unstable in the infant's normal gastric acid and are rapidly denatured[40]. Other drugs, due to their physicochemical properties are simply poorly absorbed from the gut, such as drugs which are not lipophilic or those which are very large[34]. Moreover, even after absorption many drugs undergo significant metabolism in the liver before reaching the systemic circulation[34] (first-pass effect). These barriers to absorption decrease the likelihood that significant drug concentrations will be found in the systemic circulation of the infant, and hence the likelihood of dose-related adverse reactions.

Recently, several investigators have suggested that breast milk concentrations of a drug can be predicted solely based on these physicochemical characteristics of the drug.[41,42,43]. The models which have been proposed take into account the pKa of the drug, its lipid solubility, acid-base characteristics, protein binding, along with breast milk characteristics such as fat and protein content and pH. Ito and Koren[44] have also recently extrapolated this prediction of milk concentrations to estimate the exposure to an infant by considering the clearance in infants and the normal daily dose to infants. Subsequently, I have prospectively validated this model[45] with three drugs whose breast milk concentrations were only documented after development of the models; ketoconazole, sumatriptan and methylphenidate. Actual observed concentrations correlated extremely well with the concentrations which were predicted by the models (r^2=0.99). Future studies will address additional drugs in order to strengthen the validity of the models.

Generally speaking most drugs will gain access to the breast milk in very low amounts, usually less than 10% of the maternal dose on a per kg basis (maternal weight-adjusted dose) and frequently less than 1%[46]. Because of these subclinical concentrations that will be delivered to the infant, most drugs pose little risk for use in the lactating patient. However, considering these facts, the possibility of local reactions within the gastrointestinal tract, such as diarrhea or constipation can not be ruled out. Furthermore, non-dose related reactions or idiosyncratic reactions, which may result from even extremely low concentrations in milk can not be predicted based on the concentrations of drug ingested by the infant.

1.6 Drug Therapy in the Breastfeeding Mother

With any patient treatment the physician and patient are faced with weighing the benefits of treatment against the risks. For the most part this is a fairly simple assessment because the risk of harm from a particular drug is almost always significantly less likely than risks of the untreated disease. However, when the patient of concern is lactating, the risk assessment process becomes more complex as we now have to consider two individuals. While we can be sure that treatment of the mother is more beneficial than not treating, we have to be aware that the infant may be exposed to the drug in breast milk, which may pose unnecessary harms. The obvious decision may be to withhold breastfeeding, which is frequently the advice of the treating physicians. Fortunately, only a few drugs are considered completely incompatible with breastfeeding. I have reviewed this topic elsewhere[47,48]. Moreover many women may be reluctant to discontinue breastfeeding as they are aware of the benefits that breast milk provides to their infant and the desire on their part not to lose the bonding experience that comes with breastfeeding. In addition, the costs associated with formula feeding are more than double the costs of adequate nutritional intake in a lactating mother[49,50] (V. Stevens, City of Toronto,

unpublished data, 1996), a significant deterrent to formula feeding for many. If breastfeeding is to continue, the patient and health care provider must be aware of the amounts of drug entering milk, and the possible risks of these amounts if they were to be ingested by the infant. Furthermore, these must be outweighed by the clear benefits of continuing to provide breast milk.

1.7 Difficulties Investigating the Lactating Population

Ideally, prospective, randomized controlled studies would be conducted to precisely document and investigate this population. Close monitoring of the infant and drug measurements in maternal plasma, breast milk, and infant plasma provide an accurate picture of the infant exposure and response to this exposure through breast milk. Unfortunately, practically speaking, this type of study is difficult to perform. Ethical considerations also limit feasibility since withholding treatment from patients is not reasonable. So if research can not be randomized, studies are also limited by the number of patients who actually require medication.

Even in a population of individuals highly motivated enough to participate in such a study, only a small portion will be women who require drug therapy and are concurrently lactating. Recruitment of patients is difficult, in particular since this population with newborn infants may be severely time-restricted and less willing to participate in clinical research which may hinder their time further. As a result, the information currently available to drug information services such as MotheRisk are generally limited to case reports or case series, which presents inherent bias against the null hypothesis[51].

1.8 Providing Drug Information for the Lactating Patient:

1.8.1 Review of the MotheRisk Program

The MotheRisk Program, originally a clinical consultation service began its operation in September of 1985. Some two to three years later it expanded to include a telephone consultation service, which remains its largest component to date, averaging close to 150 calls per day from across the country. It is a specialized drug information service, which provides both patients and health care providers with information about the risks and safety of drugs, chemicals, infectious diseases, and radiation in the context of pregnancy and/or lactation. A detailed description of the program is offered elsewhere[52]. Approximately 20%, or 30-35 of the daily calls to the service pertain to drugs in lactation. The service, running within the Hospital for Sick Children in Toronto, primarily counsels patients over the phone, although a small proportion of patients will come to the hospital for a clinic appointment when an exposure is of particular concern. When the initial call is placed, all patients are interviewed by trained counsellors who obtain relevant details about their medical and obstetrical history that is subsequently documented on standardized forms (Appendix A). When the caller is a health care provider as much information about the patient as possible is collected. This information includes details about the patient's medical conditions, drug use, and pregnancy history. For patients coming into the hospital clinic, a slightly more detailed medical history is taken which includes all the details in the Telephone Report Form along with information about genetic diseases and occupational exposures. This information is recorded in the clinic also on a standardized form (Appendix B). Trained counsellors and physicians document all contact with the patient as well as provide information and consultation.

Because information is collected prospectively (i.e. before the exposure to the infant has occurred), services such as MotheRisk possess unique research capabilities. By identifying maternal characteristics and drug use patterns before follow-up much of the recall bias can be eliminated, a difficulty inherent with any protocol relying on reports by human subjects.

1.8.2 Sources of Information

Services such as the MotheRisk program obtain information for a particular patient in a number of ways. These are summarized below.

1.8.2.1 Individualized Approach

For any particular risk assessment the ideal situation would be a completely individualized approach. This permits the patient to have an accurate picture of her risk potential by identifying and using information specific to her own clinical situation. This format is particularly important when there is little information about the specific drug or if the drug is exceptionally toxic even at low doses. With a series of patients contacting the MotheRisk program I have done just that[53]. Occasionally patients contacting the program who are very eager to breastfeed may be exposed to medications for which the existing information in the literature is controversial or sparse at best. This is true for exposures to lithium, amiodarone, azathioprine, and cyclosporine. For each of these exposures several patients have been provided with an individualized risk assessment, as have the child's physicians and in many cases the treating physician. This assessment has involved measurements of drugs in milk, and in infant serum whenever possible, to quantify the exposure. Milk sampling continued until all caregivers were satisfied that the safety or risk to the infant could be established. Although in some cases milk levels and infant serum concentrations of the drug were extremely high (amiodarone, cyclosporine), in most instances the levels were sufficiently low to allow for

continued breastfeeding (lithium, azathioprine, cyclosporine). This unique approach has provided all individuals involved with specific information that would not have been available from standard sources and has allowed breastfeeding to continue in cases where lack of information may have otherwise prompted the decision not to breastfeed.

1.8.2.2 Cohort Studies

Cohort studies are another source of information on which to base the patient's risk assessment. Given that few cohort studies exist in the literature with respect to drug use in breastfeeding I have used patients from the MotheRisk program to provide data on large groups of women exposed to a particular agent. I recently conducted a study on lactating patients exposed to antihistamines and examined the rate of reported adverse events in the infants[54]. In this cohort of 234 women using antihistamines while lactating, 22.6% of the mothers reported adverse events in their infants. None of the events prompted the mother to seek medical attention, suggesting that the events were not severe in nature. This information can now be used to provide adequate information to all patients in the future and large cohort studies of this nature should continue as they contribute to population-based information not normally found in the literature for this patient population.

1.8.2.3 Compiled References

Several standard references are used in providing information to the patient about the risks or safety of a particular drug while breastfeeding. The most comprehensive of these is the text edited by the WHO[46] which includes all the published references pertaining to the excretion of a particular drug in breast milk as well as express the percent exposure by the infant and summarize the effects in infants and provides recommendations. Another text, Drugs in Pregnancy and Lactation[55] also summarizes the current data without directly providing a recommendation. A book by Hale[56] along with summarizing the literature as it

pertains to use in the lactating patient will also include information about the toxicity of a particular drug in adults and in the pediatric population. It also includes many pharmacokinetic parameters of the individual drugs which may be used in the risk assessment process. Finally, every four to five years, the American Academy of Pediatrics publishes its listing "The Transfer of Drugs and Other Chemicals Into Human Milk"[4] whose recommendations are endorsed by the Canadian Pediatric Society. The publication provides recommendations on the use of drugs in a lactating patient by presenting various lists of drugs. The lists divide drugs by categories based on their relative safety. The importance of all of these references is that most health care providers treating breastfeeding mothers will have at least one, if not several of these references in their library on which they will base their recommendation to the patient. It is critical that these references accurately depict the current status of knowledge so that patients are not misinformed about their risks.

1.9 Behaviors: The Lactating Patient Taking Medication

1.9.1 The Priming Effect

Identifying positively the source of an adverse reaction as reported by the mother is difficult. Studies have clearly shown the existence of a *placebo* effect, which is the reporting of a clinical or adverse effect even in the absence of active drug[57]. A significant proportion of patients will report an adverse event even when they are given placebo probably from an anticipation that they may be on the true drug. This is reviewed by Beecher[58] who reported on this effect in several clinical studies. In the case of the lactating mother taking medication, it is conceivable that mothers are biased for an adverse event simply because of a belief that the drug will cause a reaction in her infant. One may not be totally sure if in fact the effect is due to the drug. However, Taddio et al[59] recently showed that mothers on antibiotics were no more likely to report an adverse event in the infant when explicitly counselled of a

specific reaction (primed) as compared to those who were not (unprimed). Sixty-eight percent of mothers in the primed group and 87% of mothers in the unprimed group reported events in their infants. It is not known if the act of seeking and receiving information itself can cause priming rather than the specific information provided.

1.9.2 Breastfeeding Choices

The issue of drug information for the lactating patient is an important one because it may provide the basis for which decisions regarding breastfeeding are made, particularly for women on chronic therapies.

In a cohort study on women receiving antiepileptic medications while breastfeeding (n=34),[30] I have shown that patients were significantly less likely than a healthy control group (n=34) to initiate breastfeeding (p=0.004). Patients also tended to terminate breastfeeding significantly earlier (p<0.005), despite the fact that the particular antiepileptic medications being used were considered compatible with breastfeeding[4]. In addition, the mother's choices not to breastfeed or to terminate feeding early, were frequently associated with a perception that the drugs were harmful to the infant and they reported receiving negative information from physicians about the safety of these drugs in lactation. In a smaller cohort of patients receiving propylthiouracil for hyperthyroidism (n=22)[60] I observed once again that patients were less likely to initiate breastfeeding and breastfed for a shorter duration when compared to a healthy control group (n=22). These studies have clearly highlighted the need for more evidence-based information so that patients can make appropriate decisions on their choice of feeding methods.

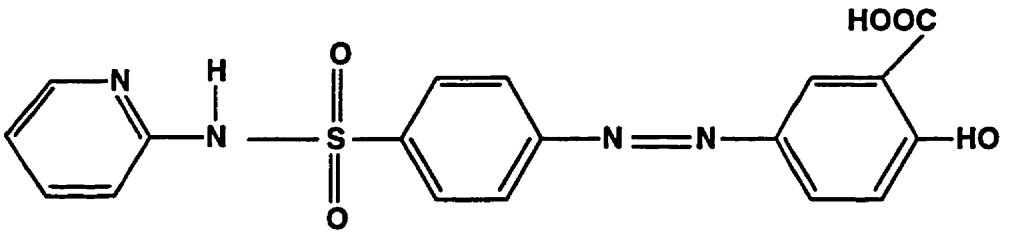
1.10 Inflammatory Bowel Disease

Inflammatory bowel disease is a group of illnesses involving a chronic inflammation in the gastrointestinal tract which has no identifiable pathogenic cause[61]. It includes diseases such as ulcerative colitis and Crohn's disease. Ulcerative colitis is characterized by diarrhea and rectal bleeding, whereas Crohn's disease is associated with anorexia and abdominal pain[61]. They can be treated symptomatically with drugs, managed by diet, or corrected with surgical removal of affected areas[61]. The onset of the disease is generally before or during childbearing years[62]. In fact, peak incidences of the disease are between 15 and 35 years of age,[5,63] thus, it is not unlikely that pregnancy and lactation will occur simultaneously with inflammatory bowel disease. Determining a precise prevalence in the general population is difficult since there appear to be differences in the rates of the diseases over time and across cities and nations[6].

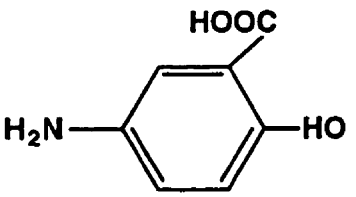
1.11 5-Aminosalicylic Acid and Related Drugs

The drugs of study in this report are 5-aminosalicylic acid (5-ASA)-containing compounds including 5-ASA, sulfasalazine and olsalazine. 5-ASA-containing drugs are used principally in the treatment of inflammatory bowel diseases such as Crohn's, ulcerative colitis, and ulcerative proctitis[64], although sulfasalazine is also effective in the treatment of rheumatoid arthritis[65]. In Canada, 5-ASA is marketed on its own or within sulfasalazine or olsalazine. They are thought to exert their activity locally in the gastrointestinal tract. Structures are shown below (Figure 1).

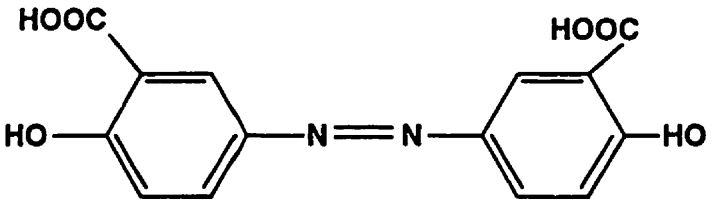
Figure 1:Structure of 5-ASA and derivatives



SULFASALAZINE



5-AMINOSALICYLIC ACID



OLSALAZINE

1.11.1 5-Aminosalicylic Acid

In Canada 5-ASA is available as Asacol®, Mesasal™, Pentasa®, Quintasa® and Salofalk®[66]. Unlike salicylic acid, 5-ASA exhibits minimal oral absorption and as such appears in very low concentrations in plasma[67] precluding its effectiveness as a systemic anti-inflammatory agent. While most of the drug is eliminated unchanged in the feces, the 20% that is absorbed, is rapidly N-acetylated in the gut wall and the liver and excreted in the urine[66]. Its plasma half life is about 0.5 to 1.5 hours[67].

5-ASA is most frequently administered orally, but may also be administered rectally in the form of a suppository or suspension enemas[67]. To avoid degradation in the stomach and upper intestine it is given a polymer coating which is pH sensitive, delaying release until the drug reaches the lower intestine,[68] where it is expected to exert its anti-inflammatory activity.

1.11.2 Sulfasalazine

Sulfasalazine is distinct in that its 5-ASA component is joined to sulfapyridine by a diazo bond[67]. It is sold in Canada as Salazopyrin®, S.A.S™ along with several generic brands[66]. In the colon, sulfasalazine is cleaved by bacteria to release 5-ASA and sulfapyridine[69] The sulfapyridine is absorbed through the colon and is approximately 10-45% bound in the plasma[70]. Along with N-acetylation, sulfapyridine is 5-hydroxylated and subsequently eliminated in the urine. Like 5-ASA, sulfapyridine has a half life of about 8 hours[71].

1.11.3 Olsalazine

Olsalazine is formed by covalent links between two 5-ASA molecules. The trade name of Olsalazine in Canada is Dipentum®[66]. Once in the gut, it is cleaved to two[72] 5-ASA molecules and will display pharmacodynamic properties similar to 5-ASA. Like 5-ASA, its properties are indicative of minimal transport into milk.

1.11.4 Toxicity of 5-Aminosalicylic Acid Containing Drugs

Toxicity and adverse reactions associated with the administration of drugs is not uncommon. 5-ASA-containing drugs are not free from side effects. Studies have shown that a fairly high proportion, 20 to 45%, of patients will report one or more side effects to sulfasalazine,[73,74] and this appears to be correlated to serum levels of sulfapyridine and to the N-acetylator phenotype[73]. The most common adverse effects include nausea, vomiting, anorexia, and headaches,[73,74] which may resolve by lowering doses or with enteric coating of tablets[75]. Since 5-ASA is free of the sulfapyridine component of the molecule, adverse events are less likely to occur[76].

1.12 Excretion of 5-ASA-Containing Drugs Into Human Milk

1.12.1 5-Aminosalicylic Acid

Small amounts of 5-ASA have been detected in milk after oral or rectal administration despite its low systemic absorption. To date, twelve reports exist in the literature characterizing the excretion of 5-ASA-containing drugs into milk or its effects on the breastfed infant. [2,3,77,78,79,80,81,82,83,84,85,86] Most of these are case reports or small case series and several do not report on infant follow-up but merely on drug levels.

The first report specifically investigating 5-ASA was a case report by Nelis[3] in which a mother had been taking 500mg suppositories of 5-ASA twice a day for her inflammatory bowel disease. Within 10 hours of administration to the mother, the breastfed infant developed watery diarrhea. Upon discontinuing the drug the infant's stool returned to normal. Rechallenge of the drug four other times revealed similar findings. The mother had been treated for ulcerative proctitis and it is possible that severe ulcerations of the colon permitted excess absorption of the drug. Breastfeeding was discontinued to permit adequate maternal treatment. Two further case reports by Jenss et al.[82], and Klotz et al.[83] did not find adverse events in the infants. Maternal doses in these reports were all orally administered, ranging from 1.5 to 3 grams per day. In one of the patients,[82] who had been taking 500 mg 5-ASA orally three times daily, the concentration of 5-ASA and its acetyl metabolite in the milk were 0.11 mg/L and 12.4 mg/L, respectively. The milk to plasma ratios were 0.27 for 5-ASA and 5.1 for acetyl-5-ASA. The second patient[83] also had very low milk concentrations of 5-ASA (0.1 mg/L) and its metabolite (12.3 to 18.1 mg/L). The infant would have ingested approximately 0.065 mg/d of the parent drug. Considering an average infant milk intake of 150 ml/kg/d[87], the infant would be expected to ingest about 0.0165 mg/kg/day 5-ASA and 1.86 mg/kg/d acetyl-5-

ASA. If we assume a maternal weight of 60 kg the infant's dose is approximately 0.066% of the maternal weight-adjusted dose. A large cohort study by Ito et al.[84] included 8 mothers who had been taking 5-ASA while lactating. There was one report of diarrhea in an infant. The final and largest report is that by Christensen et al.[86] who studied 13 patients at delivery exposed to doses of 0.5 to 3 g/d of 5-ASA. Their objective was to characterize the concentrations of the drug in maternal and infant plasma and breast milk. Only traces of 5-ASA were detectable in breast milk and follow-up of the infants was not provided.

1.12.2 Sulfasalazine

All reports of maternal exposure to sulfasalazine while breastfeeding pre-date those of 5-ASA. This is a reflection of their varied release into the market. In 1979, Jarnerot and Into-Malmberg[77] and at the same time Azad-Khan and Truelove[78] measured plasma and milk of 12 and 3 mothers, respectively. Sulfapyridine was consistently detectable, but only the latter investigators were able to detect unmetabolized sulfasalazine in milk. 5-ASA was undetectable in all samples. Berlin and Yaffe[79] had similar findings in a single patient. None of the 16 infants involved displayed adverse reactions. In 1987 Christensen et al.[80] measured amniotic fluid, maternal and chord plasma and breast milk of women who had been taking sulfasalazine near term. Sulfasalazine could not be detected in the breast milk and 5-ASA appeared in very low concentrations.

To date the only adverse reaction in an infant whose mother had been taking sulfasalazine while breastfeeding was reported by Branski et al.[2] At two months of age the infant developed bloody diarrhea which recurred two weeks later, persisting until the child was three months of age. The authors felt that the mother's drug exposure was the causative agent in this case since a full examination and work-up

of the child revealed no abnormal findings. The diarrhea resolved 48-72 hours after discontinuation of maternal drug therapy. In this case the mother was phenotyped and found to be a slow acetylator. Her serum concentrations were at the upper limit of the normal therapeutic range. Sulfapyridine was also found in the infant's blood, at 5.3 mg/L.

1.12.3 Olsalazine

Only a single report examined the excretion of olsalazine in human milk[85]. Neither olsalazine nor 5-ASA were detectable in milk and extremely low concentrations of acetyl-5-ASA were detectable in some samples. The infant did not display any adverse reactions. Although no other literature exists with specific reference to olsalazine the findings with 5-ASA will have implications for olsalazine use in the lactating patient since olsalazine is cleaved to 5-ASA in the gastrointestinal tract.

1.12.4 Specific Advice for 5-ASA Inquiries

Currently the American Academy of Pediatrics has listed 5-ASA and sulfasalazine as "Drugs that have been associated with significant effects on some nursing infants, and should be given to nursing mothers with caution"[4]. Other critical sources make similar suggestions. Briggs et al.[55], suggests that infants of mothers taking 5-ASA or olsalazine should be closely observed for changes in stool consistency, and they indicate similar cautions for sulfasalazine. The WHO text indicates that breastfeeding should proceed with caution and discontinue if diarrhea develops in the infant.[46]

At MotheRisk counsellors provide information to the patients based on a cumulative summary of the literature. That is, they are informed that the levels of excretion into milk are low (<10%) and that breastfeeding can be continued. Patients are also told

to watch the baby for any changes, as they would be for any query pertaining to drug use in lactation.

2. METHODS

2.1 Study Design:

This is a prospective, observational cohort study investigating the incidence of adverse reactions in breastfed infants whose mothers were administered 5-ASA-containing drugs while lactating.

2.1.1 The Setting

Patients were recruited from the MotheRisk Program. MotheRisk, a specialized drug information and counselling service, was the source from which subjects were selected. Essentially all patients who called the program about concerns of exposure to 5-ASA-containing drugs in pregnancy or lactation were potential subjects.

2.2 Subject Selection

All subjects were recruited from the MotheRisk program. Calls were considered potential subjects even if the initial caller was not the patient herself, provided sufficient information to permit contact with the patient was documented. Preexisting MotheRisk practices were not altered for the purposes of the study.

2.2.1 Treatment Group

All forms for patients who contacted the program about the safety of 5-ASA-containing drugs in pregnancy or lactation were eligible to be included in the treatment group. Patients were not randomized to either group since decisions about drug therapy were made by the primary care physician of each patient. Criteria for subject selection are listed in Table 1.

Table 1: Treatment Group Inclusion and Exclusion Criteria

INCLUSION CRITERIA
breastfeeding women
maternal exposure to 5-ASA-containing drugs while lactating
maternal intent to take drug therapy chronically
EXCLUSION CRITERIA
exposure to 5-ASA-containing drugs completed
previous maternal report of infant adverse event while on 5-ASA-containing drugs
babies with anatomical anomalies preventing breastfeeding
women with exposure to other drugs during lactation known to cause adverse events in infants*
women with excessive exposure to alcohol (> 2 drinks per day)
women with exposure to drugs of abuse
women not attempting to breastfeed after initial call
women unable to complete follow-up interview in english

*based on the recommendations of the American Academy of Pediatrics[4]

2.2.2 Control Group

In order to rule out possible confounding effects attributed to breastfeeding or simply to bias in maternal reports a control group was included in the study. The control group consisted of women contacting the MotheRisk program who decided

against any medication while lactating or who had trivial exposures while lactating. Trivial exposures are those which are not known to produce adverse events in a breastfed infant and were short term or acute in nature. This included analgesics such as acetaminophen, diagnostic radiation (such as dental x-rays) and topical exposures, such as hair coloring or other cosmetic products. The control group was matched with the treatment group for maternal age (± 1 year), parity and infant age at follow-up (± 4 months)

2.3 Data Collection

2.3.1 Initial Consultation

At the initial call all patients are interviewed to obtain relevant details about medical history, maternal disease and drug exposure. If the patient has already given birth to her child, details about the infant health, birth weight, gestational age at delivery, and feeding patterns are also documented (Appendix A). Calls from health care providers are documented similarly. Occasionally the initial call is followed by a visit to the hospital clinic, where the information collected is somewhat more detailed (Appendix B). After documentation, patients are counselled about their primary concern and any other issues which may arise as a result of information obtained while documenting the history. Telephone interviews generally take 8-10 minutes, while clinic consultations are 30 minutes to one hour. Patients are instructed to observe the infant for any changes and are told that a staff member may call back to conduct a follow-up interview.

2.3.2 Follow-up Interview

After all eligible patients had been retrieved they were contacted again and asked to complete the follow-up interview. This follow-up interview was completed over the

telephone in a standardized manner and information was again recorded on specifically designed forms (Appendix C). Details of the mother's medical history are confirmed as were details about the infant's health. Drug dosage regimens during lactation were re-recorded. The mother was also asked if she herself experienced adverse reactions attributable to her 5-ASA.

Feeding patterns and any problems with breastfeeding were also recorded. In an open ended manner, mothers were asked if their infant had displayed any adverse events since drug therapy had commenced. This was followed by a closed ended question assessing whether the infant had any gastrointestinal changes, stool changes or behavioral changes. Furthermore, in order to fully elucidate if there were any adverse events in the infant, the mothers were asked to recall any details about visits to a physician beyond standard visits for immunization, as well as any trips to the emergency room during the period in which she was breastfeeding and taking 5-ASA. Details about the reasons for these health care provider visits were documented.

Adverse events were defined as any changes in the infant that were a departure from that infant's normal behavior. Reports of events were based on maternal recall in most cases. If an adverse event in the infant prompted the mother to contact the child's physician, a follow-up letter (Appendix D) was sent to the relevant physician upon maternal consent. The physician was asked to confirm medical details of the course of the event and the actions taken.

Four research assistants were involved in the follow-up interview process over the course of several years as the study was being conducted. The principal investigator provided training for each of the interviewers who conducted the breastfeeding

follow-up and several also conducted pregnancy follow-up of patients who had contacted the service early in pregnancy.

Patients were also asked to report on the information they may have received with respect to their drug use in breastfeeding and from whom this information came. A source was defined as any individual who was consulted about these effects; this may have been the patient's physician, another healthcare provider, friends or family members, the media or MotheRisk. The source's information was classified into three categories, that is, positive, negative, or discordant. If all sources the patient consulted indicated that the drug was safe, her information was said to be positive. If all sources she consulted indicated a lack of safety, her information was classified as negative, and if she received differing information among the sources her information was classified as discordant.

2.4 Data Analysis

Statistical analysis was performed on the data whenever possible although some data were expressed in a descriptive manner. Most data were analyzed using the Statview computer program [88] or the EpiInfo[89] epidemiologic data analysis software.

2.4.1 Testing of Hypothesis

In order to determine differences between the treatment and control groups statistical analysis was performed. Non-continuous data were analyzed using the Chi square test and Fisher's exact test for 2 x 2 tables. Variables considered include parity, rates of discontinued breastfeeding, problems with breastfeeding, the infant's medical conditions, and proportion of adverse events. Continuous variables were analyzed using Mann-Whitney U test for non-parametric data (not normally distributed), and unpaired Student's t-test for parametric (normally distributed) data.

Continuous variables included maternal age, infant age at follow-up, time to introduce formula and duration of breastfeeding. A p-value of 0.05 was considered significant.

2.4.2 Differences Between Group Reporting Adverse Events and Not Reporting Adverse Events

When comparing the group in which the mother had reported an adverse event in the child to the group which did not report an adverse event in the child, rates and proportions (parity, report of maternal adverse effect, indication, brand of drug used) were compared using the Chi square test or Fisher's Exact test as appropriate. Relative risks with 95% confidence intervals were also calculated. For continuous data, which includes duration of breastfeeding, number of sources consulted, infant age at follow-up, time to introduce formula, duration of breastfeeding and duration of infant exposure to drug through milk, Mann-Whitney U test was used, except in cases where data was normally distributed. Unpaired student's t-test was used for these variables. All continuous data are expressed as means ± standard deviation (SD) and categorical data is expressed as raw values and as a percent of the total. Ranges are indicated when relevant.

3. RESULTS

3.1 Study Population

A total of 121 women were recruited into the treatment group of the study. There were also 121 breastfeeding controls followed, for a total of 242 mother-infant pairs.

3.1.1 Treatment Group: Characteristics

Within the group of mother-infant pairs exposed to 5-ASA-containing drugs there were 117 exposures to 5-ASA, 2 to sulfasalazine and 2 to olsalazine. For women taking 5-ASA the average daily maternal dose was 2065 ± 1277 mg per day. The group exposed to 5-ASA were taking a variety of brands of this particular drug (Table 2).

Table 2: Distribution of Drug Used

Exposure	n=121
5-ASA	60 (49.6 %) Asacol®
[Total 117 (95.9%)]	28 (23.1 %) Pentasa®
	20 (16.5 %) Salofalk®
	8 (6.6 %) Mesasal™
	1 (0.8 %) Unknown*
Sulfasalazine	2 (1.6%)
Olsalazine	2 (1.6%)

* 1 brand name not reported by mother

The indication for using these medications is listed below for women within the treatment group (Table 3).

Table 3 : Indication for medication in treatment group (n=121)

5-ASA		sulfasalazine	olsalazine
66 (54.5%)	ulcerative colitis	2 (1.7%) ulcerative colitis	2 (1.7%) ulcerative colitis
8 (6.6%)	ulcerative proctitis		
43 (35.5%)	Crohn's Disease		

Not all women had been taking the drug chronically. Some women had been taking the drug throughout pregnancy, whereas others started drug therapy after the birth of the child (Table 4). In the postnatal period infants were exposed to the drug through milk for a mean of 5.3 ± 4.7 months (range: 3 days-24 months).

Table 4: Exposure timing of maternal drug therapy

Pregnancy and post-partum	post-partum only
96/121 (79.3%)	25 (20.7%)

3.2 Group Demographics

3.2.1 Maternal Characteristics

There were no significant differences in the maternal characteristics between the treatment and control groups (Table 5)

Table 5: Maternal Characteristics - Treatment vs. Control Group

		Treatment Group	Control Group	p-value
Maternal Age		31.5 ± 4.0	31.6 ± 3.9	0.82
Parity:	P=1	54%	41%	
	P=2	32%	43%	0.21
Problems with Breast Feeding (% No)		75%	82%	0.16

3.2.2 Infant Characteristics

There were no significant differences in the infant characteristics between the treatment and control groups (Table 6).

Table 6: Infant Characteristics - Treatment vs. Control Group

	Treatment Group	Control Group	p-value
Infants age at Follow-Up (mos)	22.0 ± 20.2	20.9 ± 18.1	0.65
Infant Medical Condition? (%Yes)	91%	87%	0.29

Mothers reported on any underlying medical conditions which are described in Table 7.

Table 7: Health Problems in Infants as Reported by the Mother

Treatment Group	Control Group
sublingual thyroid	heart murmur
lactose intolerant	kidney problem
recurrent UTIs	seizures (3)
seizures	hypoglycemic
level II heart murmur	lactose intolerant
	hyperactive
	breathing problems
	cystic fibrosis
	asthma (4)
	tubes in ears
	Marcus-Gunn Jaw wink
	cerebral palsey
	hematoma

3.3 Maternal Behaviors

3.3.1 Sources of Information

Mothers reported on the number of sources they consulted for issues surrounding breastfeeding. The sources included health care providers, family/friends, the media and MotheRisk. For women in the treatment group and women in the control group with innocuous exposures, these sources would have specifically been consulted regarding the safety of lactating while using the particular medication (Table 8). Women in the Treatment group reported consulting significantly more sources that those in the Control Group although the type of information they received did not differ overall.

Table 8: Sources of Information

		Treatment Group (n=79)	Control Group (n=79)	p-value
Number of Sources Consulted		3.15 ± 1.35	2.57 ± 1.68	0.01
	(range)	(1-6)	(0-5)	
Type of Advice	Positive	47 (59.5%)	49 (62.0%)	0.95
	Negative	1 (1.3%)	1 (1.3%)	
	Discordant	31(39.3%)	29 (35.7%)	

3.3.2 Reasons for Discontinuing Medication

A total of 32 (26.4%) women in the treatment group had discontinued medication by the time of the follow-up interview. The reasons for such are categorized on Table 9.

Table 9: Reasons for Discontinuation of 5-ASA Therapy

Reason Given	n=31*
Medication No Longer Needed	19 (61.2%)
Medication Not Effective	3 (9.7%)
Concerned About the Health of Infant	3 (9.7%)
Maternal Adverse Reaction	3 (9.7%)
Others	3 (9.7%)

*data not available in 1 case

3.3.3 Breast Feeding Patterns

A proportion of women in each group had discontinued breastfeeding by the time of follow-up. The rate of those who had discontinued breastfeeding was not significantly different between the two groups. When analyzing the mean duration of breastfeeding in cases where breastfeeding was discontinued there was no significant difference between the two groups. The breastfeeding duration analysis was performed again, this time including all patients. In cases where the infant was still being breastfed the age at follow-up was used. There was no statistically significant difference (Table 10). Within the treatment group only three women specifically stated that they had stopped breastfeeding to resume drug therapy.

Table 10: Breast feeding trends - Treatment Group vs. Control Group

	Treatment Group	Control Group	p-value
No Longer Breastfeeding	83 (67%)	85 (70%)	0.13
Duration of Breast feeding- entire cohort (mos)	7.4 ± 6.0	7.3 ± 5.5	0.72
Duration of Breastfeeding- baby no longer breastfeeding (mos)	6.8 ± 5.4	6.1 ± 4.4	0.61
Time to Introduce Formula	3.6 ± 2.7	3.5 ± 2.8	0.64

3.4 Adverse Event Outcomes

Analysis of the rates of adverse events in the infant as reported by the mothers did not reveal significant differences between the two groups (Table 11). The mean age of the infants at onset of the adverse event was also not significantly different between the Treatment and Control groups.

Table 11: Adverse Events as Reported by the Mother

		Treatment Group		Control Group		p-value
Infant Adverse Events	Yes	14	(12%)	13	(11%)	0.84*
	No	107	(88%)	108	(89%)	
Infant Age at Onset of Event (mos)		2.0 ± 2.1†		3.6 ± 5.1‡		0.41

*Relative Risk (95% CI)=1.08 (0.5-2.19)
† explicit data available for only 9 cases
‡ explicit data available for only 12 cases

The list of adverse events is seen in Table 12. There was 1 case of blood and mucus in stool reported in each group. There were no other cases of diarrhea reported in

the treatment group, however there was an additional case of bloody diarrhea in the control group as well as 3 other cases of diarrhea.

Table 12: List of Adverse Events Reported in Infants

Treatment	Control
4 (3.3%) colic	5 (4.1%) colic
3 (2.5%) constipation	3 (2.5%) eczema
3 (2.5%) gas	3 (2.5%) diarrhea
1 (0.8%) blood and mucus in stool	1 (0.8%) bloody diarrhea
1 (0.8%) infant spitting up mucus	1 (0.8%) blood and mucus in stool
1 (0.8%) eczema	
1 (0.8%) green stool	

Within the treatment group 8 (10.9%) of the mothers reported experiencing side effects to the drugs themselves.

3.4.1 Power Calculation

Although the rates of all adverse events in breastfed infants are not known, the study power has been calculated using the rate of adverse events observed in the control group (11%). The power of the study to detect at two fold increase in the rate of infant adverse events was 57%, with a 5% level of significance.

3.4.2 Characteristics Of Patients Reporting Adverse Events In Infants vs. Patients Not Reporting Adverse Events In Infants

Possible confounding variables were examined for their potential effect on the incidence of reported adverse events. In Table 13, examining the entire cohort of mother-infant pairs revealed that maternal parity was not significantly different in

the group reporting adverse events as compared to the group not reporting adverse events. Furthermore, women reporting side effects in themselves were no more likely to report an adverse event in their infants as compared to women not experiencing adverse effects from the drug, with a relative risk (95% confidence interval) of 0.48 (0.07-3.47). There were no significant differences in maternal age, duration of breastfeeding, time to introduce formula feeding, and the number of sources consulted by the patient between the "Infant Adverse Event" and "Infant No Adverse Event" groups. However, the infants in whom an adverse event was reported were significantly younger at follow-up than those not reporting adverse events (Table 13).

Table 13: Characteristics of Subjects Reporting Adverse Events in Infants and Subjects Not Reporting Adverse Events - Whole Cohort (n=242)

	Infant Adverse Event (n=27)	Infant No Adverse Event (n=215)	p-value
Maternal parity P=1	11 (40.7%)	104 (48.4%)	0.42
P=2	9 (33.3%)	82 (38.1%)	
P>2	7 (26%)	29 (13.5%)	
Maternal Adverse Effect Yes	1 (7.7%)	18 (15.7%)	0.69§
No	12 (92.3%) †	97 (84.3%) ‡	
Maternal Age	32.1 ± 3.7	31.4 ± 4.0	0.37
Infant Age at Follow-Up (mos)	13.7 ± 10.6	22.4 ± 19.8	**0.02**
Duration of Breast Feeding (mos)	7.5 ± 6.2	7.3 ± 5.7	0.86
Time to Introduce Formula (mos)	3.1 ± 3.1	3.5 ± 2.7	0.51
Number of Sources consulted	2.9 ± 1.7	2.8 ± 1.3	0.86

† data not available for 14 cases
‡ data not available for 100 cases
§ Relative Risk (95% CI) = 0.48 (0.07-3.47)

Focusing on the treatment group, a similar comparison was performed between the adverse event group and the no adverse event group, revealing different findings. (Table 14). Maternal parity was not different in the women reporting adverse events in their infants as compared to the women not reporting adverse events. Women reporting adverse events were no more likely to be taking any particular brand of 5-ASA, have any specific indication for drug therapy or to have reported an adverse effect due to drug therapy in themselves. Mothers were of similar age, were consuming similar doses of 5-ASA, consulted a similar number of sources regarding the safety of their drug use while breastfeeding and received similar advice. Although not statistically significant, mothers reporting adverse events in their children tended to introduce formula as a supplement to the infants diet somewhat sooner than those who did not. The infant age at follow-up was significant once again as was the duration of breastfeeding, with women reporting adverse events breastfeeding for a shorter period.

When the analysis was performed with the control group only the infant age at follow-up was not significantly different between the Infant Adverse Event and Infant No Adverse Event groups ($p=0.47$). However the Adverse Event group was slightly younger (17.5 vs 21.3), although the standard deviations were large; greater than half the mean.

Table 14: Characteristics of Subjects Reporting Adverse Events in Infants and Subjects Not Reporting Adverse Events - Treatment Group Only (n=121)

		Infant Adverse Event (n=14)	Infant No Adverse Event (n=107)	p-value
Maternal parity	P=1	6 (42.9%)	59 (55.1%)	0.90
	P=2	5 (35.7%)	34 (31.8%)	
	P>2	3 (21.4%)	14 (13.1%)	
Maternal Adverse Effect	Yes	1 (12.5%)	11 (16.9%)	>0.99*
	No	7 (87.5%)†	54 (83.1%)‡	
Drug Brand	Asacol®	6 (46.1%)	54 (50.5%)	0.35
	Mesasal™	0	8 (7.5%)	
	Pentasa®	5 (38.5%)	23 (21.5%)	
	Salofalk®	1 (7.7%)	19 (17.8%)	
	Salazopyrin®	1 (7.7%)	1 (0.9%)	
	Dipentum®	0	2 (1.8%)	
Indication	ulcerative colitis	8 (57.1%)	62 (57.9%)	0.99
	ulcerative proctitis	1 (7.1%)	7 (6.5%)	
	Crohn's	5 (35.7%)	38 (35.5%)	
Dose of Drug (mg)		1811 ± 1398	2099 ± 1264	0.44
Duration of Infant Exposure		3.0 ± 2.1	5.7 ± 4.8	**0.04**
Maternal Age		31.6 ± 3.8	31.4 ± 4.0	0.91
Infant Age at Follow-Up (mos)		10.2 ± 8.1	23.5 ± 20.8	**0.01**
Duration of Breast Feeding (mos)		4.1 ± 3.3	7.8 ± 6.2	**0.03**
Time to Introduce Formula (mos)		2.3 ± 2.7	3.8 ± 2.6	0.51
Number of Sources consulted		3.5 ± 1.6	3.1 ± 1.3	0.26
Type of Advice	Positive	8 (17.0%)	39 (59.1%)	0.07
	Negative	1 (7.7 %)	0	
	Discordant	4 (30.8%)	27 (40.9%)¥	

† data not available for 6 cases, ‡ data not available for 42 cases
* Relative Risk (95% CI) = 0.74 (0.11-4.99)
¥ data not available for 41 cases

4. DISCUSSION

4.1 Findings - Null Hypothesis Not Rejected

Maternal therapy with 5-ASA-containing drugs while lactating did not appear to be associated with major adverse events in their breastfeeding infants. Although there were few cases similar to those previously reported in the literature (Section 1.12), the non-treated group also reported a similar incidence of adverse events in their infants. This finding suggests that, within the limited power of this cohort, there is no increased risk of adverse events attributable to 5-ASA exposure through milk. Moreover, the adverse events most similar to those reported in the literature occurred in both groups, with a higher rate of these specific gastrointestinal events seen in the control group.

Descriptions below indicate that most of the infant events can not be directly attributed to drug exposure through milk for a variety of reasons which are commented on throughout (see Section 4.1.1.1). The events in the control group are also described (see Section 4.1.1.2) to highlight that, in fact, many reports by the mother are quite similar to those in the treatment group. This further supports the notion that these events may have occurred spontaneously even in the absence of maternal drug use. This data has not been able to support the reports in the literature that 5-ASA is a causative agent in diarrhea or bloody diarrhea in infants whose mothers were taking the drug while lactating.

The manner in which the patients were initially counselled on the effects of this drug while breastfeeding may also have affected reporting. If the patient's perception that the likelihood of an adverse event was small they may have been less likely to note a particular event and report it to the interviewer at follow-up. Taddio et al.[59] did show that the type of counselling did not affect the likelihood of reporting an adverse event, however the act of seeking counselling itself may have bearing on the tendency to report an adverse event. This tendency can not be elucidated from this group since all patients sought counselling of some type.

4.1.1 Description of Reported Infant Adverse Events

4.1.1.1 Treatment Group

colic (Case # 9)

The patient had been taking 1000 mg/d sulfasalazine for ulcerative colitis. The follow-up was conducted when the child was 12 months of age and the mother reported colic occurring when the child was about 1 month old. She did not seek medical attention for this event and breastfeeding was continued until four months of age. This mother had also reported that she herself experienced adverse effects from the drug therapy and she consulted 6 sources about the use of this drug while lactating. These six sources provided inconsistent information and as a result the mother was left with controversial advice and possibly a misperception of risk to her infant. It is also possible that her reporting of an adverse event predisposed her to reporting an event in her child.

blood and mucus in stool (Case #28)

This was a report by a mother who had been taking 1200 mg/d of 5-ASA (Asacol®) for ulcerative colitis. Follow-up was conducted at 22 months of age. The mother observed blood and mucus in the baby's stool on one occasion when the child was 2 weeks old. This resolved spontaneously so the mother did not seek medical attention. She continued to breastfeed until the baby was six and a half months old and had received information about the use of her drug from 5 different sources while lactating. All of them were reassuring and indicated that breastfeeding was considered safe. If in fact this event was caused by 5-ASA it would likely have recurred since drug therapy was not discontinued.

colic at birth and constipation (Case #29)

This infant was exposed to 5-ASA (Asacol®) from a mother who had Crohn's disease and was taking 1500 mg/d. Follow-up occurred when the infant was almost 24 months of age. Follow-up indicated that the infant was colicky at 1 month of age. She did not speak to the child's physician about this. The mother discontinued breastfeeding 1 week later. She had consulted four sources regarding the effects of breastfeeding while taking 5-ASA, which gave her controversial advice.

dispelling mucus (Case #33)

In this case, the mother was taking 5-ASA (Asacol®), 1000 mg/d for ulcerative proctitis. Follow-up was conducted at 14 months of age and the mother had continued to breastfeed for nine months but had discontinued drug therapy in three days because of concerns arising from the adverse reaction in the infant. However, after discontinuing drug therapy the mother reported that the dispelling of mucus recurred two more times. It is unlikely that this event can be attributed to drug therapy since it did not resolve after discontinuation of treatment. This mother had

consulted three sources of information about drug therapy while lactating , which were controversial.

colic (Case #75)

This mother was contacted 2.5 months after the birth of her child. She had been taking 5-ASA (Salofalk®), 500 mg/d for ulcerative colitis. The mother had spoken to 4 sources regarding information about the drug use in lactation; all of these were positive. The mother reported colic in the infant which appeared to be getting better. She was still taking the medication and breastfeeding at the time and felt that the colic was simply a factor of the child's age.

colic (Case #76)

This follow-up was conducted when the infant was 2 months of age. The mother was taking 500 mg/d of 5-ASA (Pentasa®) for Crohn's. Although she discontinued breastfeeding she reported that this was attributable to the severity of her illness. She had consulted six sources about drug therapy while lactating and all were positive. She did report that the colic had resolved. Since infant exposure was discontinued it is difficult to interpret the causative agent in this case. Exposure to the drug through milk can not be ruled out.

eczema (Case #100)

This follow-up was of an 18 month old infant. The mother breastfed for 3 months and was taking 5-ASA (Asacol®) at 4000 mg/d for ulcerative colitis. She reported that the infant had eczema. A causative effect of the drug can not be ruled out in this case.

gassy (Case #184)

This 1.5 month old infant who was still being breastfed at the time of follow-up. The mother was taking 4000 mg/d of 5-ASA (Pentasa®) for Crohn's disease. She reported that the infant was experiencing gastrointestinal disturbances (gassy). Four sources had been consulted regarding the safety of breastfeeding while taking this medication and they provided the mother with controversial input. An allergic reaction caused by the drug is a possibility in this case; however, the patient's mother did not consult a physician.

green stool (Case #190)

At follow-up this infant was almost 2 months old and was still being breastfed, mother was taking 600 mg/d of 5-ASA (Asacol®) for ulcerative colitis. She reported that the infant's stool was unusual (green in colour). Both of the sources she had consulted gave her positive information about the safety of breastfeeding while taking this drug. Effects of the drug also can not be ruled out and a physician was not yet consulted about the matter.

gassy (Case #191)

This is the case of an infant who was followed-up at 16 months of age. The mother was taking 1000-1500 mg/d of 5-ASA (Asacol®) for ulcerative colitis. She reported that she discontinued breastfeeding because of insufficient milk and the baby had been gassy just shortly before that. The gassiness resolved, however since breastfeeding was also discontinued at the same time a drug effect can not be ruled out. No physician was consulted about the event but all three of the sources the mother contacted about the safety while breastfeeding were supportive.

constipated (Case #197)

The mother of this infant reported an episode of constipation which resolved with the administration of gripe water to the infant. The mother was still breastfeeding the infant at follow-up which was conducted at 5.25 months of age. She also continued to take her medication sulfasalazine, 3000 mg/d for ulcerative colitis. It is unlikely that this constipation was due to the drug use since the event resolved despite continued maternal drug therapy. A physician was not consulted about the event however the mother had contacted one source about the safety of breastfeeding which was negative.

colic (Case #202)

In another case of colic reported, the infant was still colicky at follow-up (5.75 months of age). The mother was also still breastfeeding and taking 5-ASA (Pentasa®) at 4000 mg/d for Crohn's disease. She had consulted two sources who both gave positive information pertaining to using this drug while lactating. The child's physician was not consulted about this event.

constipated (Case #203)

This report of constipation occurred when the infant was 16 months of age. The child had been breastfed for 12 months and the mother was taking 5-ASA (Pentasa®) for Crohn's disease. The four sources of information provided to her were all positive with respect to the use of this drug during lactation. She reported that the constipation resolved with no intervention or medical attention. A causative effect of 5-ASA is unlikely in this case.

gassy (Case #204)

This follow-up was conducted when the infant was 1.5 months of age. The mother was taking 1000 mg/d of 5-ASA (Pentasa®). The gassiness in the infant persisted

and she was still breastfeeding. The mother had received positive information about breastfeeding from two sources and attributed the event in her child to insufficient milk.

4.1.1.2 Control Group

diarrhea-green stool (Case #46)

A report of diarrhea when the infant was 4 months of age. The infant was 23 months at follow-up. The event resolved without medical attention and the child continued to breastfeed until 17 months of age.

colic (Case #59)

This case of colic was reported at 28 months of age. The child had been breastfed for 9 months and the colic resolved, no consultation with a physician was necessary.

colic (Case #86)

This was a report of colic in an infant which resolved spontaneously. The infant had been breastfed until 16 months of age and the follow-up was conducted when the child was 48 months old

eczema (Case #149)

A child who was still being breastfed at 25 months was reported to have eczema which persisted.

colic (Case #156)

A follow-up indicated an infant who displayed colic for 10 months. The child was breastfed for 6 months and followed-up at 14 months.

blood in stool (Case #176)

This report of blood in the infant's stool was received at follow-up which was conducted when the child was 14 months of age. The event, which occurred in the first weeks of life, resolved when the mother stopped drinking milk at the suggestion of a physician. The child continued to breastfeed until 10 months of age with no further events.

eczema (Case # 180)

The mother in this case reported eczema in her child which occurred each time the child was given antibiotics. The mother continued to breastfeed and follow-up was conducted at 9.5 months of age.

diarrhea (Case #209)

This event of diarrhea occurred when the infant was 6 months of age, when solids were introduced. Follow-up was conducted at 11 months of age and the mother was still breastfeeding.

colic (Case #212)

This infant was reported to be colicky at birth which resolved at 4 months of age. Follow-up was conducted at 16 months of age and the infant had been breastfed until 10 months.

eczema (Case #213)

This is a report of an infant with eczema around birth. The infant was 6 months at follow-up and was still being breastfed. The eczema resolved when the mother changed laundry detergent.

bloody diarrhea (Case #215)

This follow-up conducted at 3.25 months of age, was of an infant who was still being breastfed. The infant had a single episode of bloody diarrhea at 9 days of life which did not recur.

diarrhea (Case #222)

A case of diarrhea was reported at follow-up of a 21 month old infant who was still being breastfed. The event occurred at 18 months of age and although the child's physician was consulted the diarrhea resolved spontaneously.

colic (Case #229)

Colic was reported at 2 months of age in an infant who was followed-up at 8 months. The colic did resolve and the infant was still being breastfed.

4.2 Characteristics Associated With an Increased Incidence of Reporting Adverse Events

Detailed analysis of the patient population has revealed that several characteristics may distinguish mothers reporting adverse events or their behaviors, with respect to breastfeeding. Analysis performed on the whole cohort as well as sub-analysis of the cohort of women exposed to 5-ASA-containing drugs demonstrated that adverse events were more likely to be reported when the infant follow-up was conducted at a younger age. This suggests that recall is affected over time, such that mothers may have more difficulty reporting an event the longer the time that has elapsed since it occurred. This finding is corroborated in the literature[90] as is in fact true of any study which relies on patient recall of events.

These mothers reporting adverse events in their infants were no more likely to have reported an adverse effect in themselves due to the drug. Surprisingly, this finding contradicts those by Taddio et al.[91], which demonstrated that women who experienced adverse effects from short-term antibiotic therapy were significantly more likely to have reported adverse events in their breastfed infants. This may be explained by the nature of the maternal exposure in this investigation. All mothers in the treatment group were women who had a chronic illness requiring long term therapy with medication. Women may have become accustomed, over the course of years of treatment, to the effects of the drug and, as an oversight, may not have reported the side effect. Alternatively, the cohort of women in this study may have been an inherently select group compared with those studied by Taddio et al.[59],who tolerate the drug therapy well and simply did not experience adverse effects. Patients not tolerating drug therapy and experiencing adverse effects may have discontinued their use and hence were not eligible for selection in this group. In addition, the study population may have inadvertently selected a group of women with less severe disease who are not likely to have adverse effects. If maternal disease was extremely severe, drug dosages high and polydrug therapy indicated, patients may have elected not to breastfeed at all because of overwhelming concerns, and once again, not being represented in the study population. Although we did not see differences in the maternal drug doses in the "adverse event group" as compared with the "no adverse event group" the mean maternal doses in our cohort were lower than the dose customarily used for maintenance treatment of inflammatory bowel disease.

Characteristics, such as parity, maternal age, and sources of information consulted, did not appear to have any effect on the reporting of adverse events in the whole cohort or in the subgroup of exposed patients only. Within the treatment group drug

brand used, dose, and indication for therapy also did not appear to influence the likelihood of reporting an adverse event.

The reporting of adverse events did not influence the age at which formula was introduced in the whole cohort. However, there was a tendency in the treatment group to introduce formula at a younger age when an adverse event was reported. This suggests that maternal disease and medication use may in fact be perceived by the patient as a risk to the infant, despite the fact that only one patient explicitly mentioned discontinuing breastfeeding because of concerns arising from an adverse event. In order to minimize this risk, patients in the treatment group introduced formula sooner, thereby decreasing duration of exclusive breastfeeding, and subsequently decreasing the infant's exposure to drug in milk.

These findings are further supported by analysis within the treatment group, of breastfeeding duration, number of sources consulted, and duration of infant exposure to drug through milk . Both breastfeeding duration and duration of infant exposure were found to be lower in the group reporting adverse events, whereas women reporting adverse events were more likely to have consulted more sources of information. This suggests that the concerns about risk to the infant may manifest themselves in altered behaviors by the mother. Although in many cases, the mother did not consult a physician (4.1.1) she may have attempted to minimize risk by decreasing the duration of breastfeeding and/or drug therapy. The increase in sources consulted presents an interesting inference, that is, women who have consulted too many sources may become confused by discordant information or overwhelmed by the information reported and as a result were more likely to observe adverse events. Although not significant, there was a tendency for the exposed group who reported adverse events in their children to have received

negative information. Unfortunately the sample size is too small in this case to draw conclusions from the finding.

4.3 Comparison to Other Cohort Studies of Drug Use During Lactation

To date few investigators have performed studies such as that reported here. As mentioned previously, most reports in the literature concerning effects of drug use in the lactating population consist of case reports and small case series. MotheRisk is uniquely providing information in this area with large-scale studies on this population of women and children[1,30,54,59,84]. However, none of these studies to date have specifically compared reported adverse event rates in a group of mother-infant pairs with chronic exposure to a particular medication to a group not having such exposure.

Interestingly, the rate of adverse events observed in this investigation is significantly lower than that reported previously by this group,[84,59] although the age at follow-up in this cohort is significantly older than in the previous studies. In these reports follow-up was conducted days to weeks after the initial interview which may have significantly affected the rate of adverse events reported. This is strongly supported by the existing data which did show that the rate of adverse events reported was lower over time.

The previous studies, which did not have a control group without exposures to the drug in question, were not able to determine the rate of what appears to be adverse events due to factors other than the drug itself. Coupled with the previous study from our group[84], this study clearly indicates about one in 10 nursing women notice some clinical events in their infants even though they are not receiving any drug.

4.4 Limitations

4.4.1 Sample Selection and Study Setting

This study is limited by the nature of the patient population. That is, all patients had to have contacted the MotheRisk program for some type of counselling and drug information. The control group however, was selected in the same manner which provides internal validity. However, these patients represent a highly motivated group which may not adequately reflect the general breastfeeding population. Their perception of risk may be elevated above those in the general population which may have instigated their initial contact with the program.

The setting, MotheRisk, also presents a limitation because patients not contacting the program can not be identified or described. Previous studies from this group[30] have shown that callers to the program generally represent a middle to upper class population which clearly does not reflect the population at large. On the other hand, patients of a lower socioeconomic class may have more reason to report adverse events such as diarrhea or bloody diarrhea, because of other risk factors, namely a higher risk for infectious disease in the infant. It is possible that these risks may have confounded the reported rates.

4.4.2 Maternal Recall Bias

As with any study relying on reports from patients, recall bias is a limitation. Patients frequently are unable to recall events or may misrepresent an event since their recall of the event will diminish over time. This "diminished recall over time" is shown by the findings of this report. A recent report attempted to show that patient's recall would corroborate the information documented in the patient's chart[92]. Although they found that patients accurately reported quantitative data,

such as birth weight and gestational age at delivery, they were less effective in reporting qualitative data such as pregnancy complications and post-natal complications. Therefore, the absolute incidence of adverse events observed in this study may be subject to this bias. However, since the control group is followed in the same manner, it is subject to the same bias and the comparison becomes a valid one. Moreover, it is reassuring to note that even in the presence of this bias, few events required medical attention and no event persisted or resulted in severe infant morbidity.

4.4.3 Study Power

The rate of clinical adverse events in all breastfeeding infants is not known. If the rate is assumed to be that observed in the control group then the power of this study to detect a two-fold increase in the rate of adverse events was 57%, with a 5% level of significance. To detect a two-fold increase in the rate of adverse events with 80% power the study sample size would have to be increased to 392 (196 in each group).

Studies have investigated the risks of diarrhea in infants at various stages in life and in different countries. The rates of diarrhea in developing nations is extremely high, usually due to infectious agents which are much less a risk factor in industrialized nations,[93] and as a result the risks would be much lower in Canada. A very large study conducted by Howie et al.[94] indicated that the risk of hospitalization due to gastrointestinal illness in infants who were breastfed for more than 3 months was 2%. Based on this value and the number of patients studied, this study is able to rule out a six-fold increase in the rate of hospitalizations due to gastrointestinal illness, with a power of 80% and a 5% level of significance.

4.5 Future Research

This large-scale study has provided reassuring data about the safety of 5-ASA-containing drugs, mainly the pure 5-ASA formulation, in the breastfeeding patient. In most industrialized nations, including Canada, more than 80% of women start breastfeeding[25]. It is important to examine the current incidence of breastfeeding in women receiving 5-ASA, and to determine whether dissemination of the present findings can change the epidemiology of breastfeeding prevalence in this group of patient.

Since follow-up interview style and content may affect maternal report, future studies of this type should aim to develop more structured response forms. As well, patient diaries and decreasing the time for subsequent follow-up will increase the accuracy of the reported outcomes and strengthen the findings of the report. These tools may be useful in other large-scale studies of drug use in lactating patients. In particular, drugs that are currently considered controversial for use in this population, due to serious cases in the literature, should be addressed in this manner.

4.6 Impact On Patient and Clinician

The data presented herein are reassuring for both the patient and the clinician. Patients needing drug therapy with 5-ASA for inflammatory bowel disease can safely take their medication. Clinicians faced with the decision on whether to advise a patient requiring drug therapy to breastfeed are provided with results that suggest that infants whose mothers are taking 5-ASA while breastfeeding are very unlikely to experience drug related adverse events. Idiosyncratic reports in the literature, however, were quite severe. Because this type of reaction can not be

predicted, patients should still be counselled to observe the infant whenever the mother is taking 5-ASA while breastfeeding.

5. CONCLUSION

Drug therapy in the lactating patient provides unique challenges in risk assessment since the risk of exposure of an infant to a drug in milk must be outweighed by both the benefits of continued breastfeeding and of appropriate treatment of maternal disease. This assessment is particularly difficult when literature reports suggest there may be concerns, and adverse effects have been observed clinically in infants whose mothers were taking the medication while breastfeeding.

This study has measured the rates of adverse events in infants whose mothers had been taking 5-ASA-containing drugs while breastfeeding. After an initial call to a counselling service, patients were contacted at a later date to ascertain details pertaining to drug use and the occurrence of any adverse events. A control group was followed similarly. There was no difference in the reported adverse events in the treatment group compared to the control group. This suggests that, based on the power of this sample size, the use of 5-ASA during lactation is not associated with a significant risk to the breastfed infant. Moreover, the specific incidence of diarrhea or bloody diarrhea was also not different in the two groups, suggesting that the likelihood of this particular event, as described in the literature, is uncommon.

These findings are significant since this study is the first large-scale study examining the effects of 5-ASA on the breastfed infant which has demonstrated no

appreciable risk attributable to 5-ASA-containing drugs. Since 5-ASA is generally chronically administered, these data have notable clinical relevance to a select population of patients who can be reassured by these data. The results are also relevant to MotheRisk, which provides this information to patients and healthcare providers on a daily basis. Future studies addressing the incidence of breastfeeding initiation in these women may determine if the information reported in this study affects willingness to breastfeed.

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Appendix A: Telephone Report Form

MOTHE RISK IntakeForm

I.D. #_____
Intake ddmmyyXXXX

DEMOGRAPHICS

Patient's Name_____

Home phone_____ Work phone_____

Date of birth _____ Amnio? Yes○ No○ Advised○

Referred by:_____ Health card #_____

Stable contact #_____ relationship:_____

Current M.D./type: _____ phone: _____

Occupation:

INCOMING:
date: _____ time: _____
counsellor: _____
completed ○ passed to fellow○
OUTGOING:
date: _____ time: _____
completed by: _____

CALLER _____
Contact number _____
Identity: _____

PREGNANCY

NOT PREGNANT general info○ planning ○
retrospective○ breastfeeding ○

LMP (d/m/y) _____ every ____ days Certain? Y N

Currently: weight____ kg lb gestation ____ wk mos

EDC (d/m/y) by dates ○ by ultrasound ○

G___ P___ SA___ TA___

defects in previous pregnancies? No ○Yes_____

Most recent ultrasound in current pregnancy: Not yet ○
at weeks Reason: Results:

MEDICAL HISTORY

Kidney	No○	Yes_____
Heart	No○	Yes_____
Hypertension	No○	Yes_____
Diabetes	No○	Yes_____
Respiratory	No○	Yes_____
Thyroid	No○	Yes_____
Psychiatric	No○	Yes_____
Epilepsy	No○	Yes_____

Vitamin supplementation? No○ Yes: _____
Other _____

EXPOSURE

DRUG *Infections & Chemicals - on reverse*	Start	Stop	Dose / Route	Indication	Advice as per MR statement
	○ not yet	○ ongoing			
	○ not yet	○ ongoing			
	○ not yet	○ ongoing			
	○ not yet	○ ongoing			
	○ not yet	○ ongoing			
	○ not yet	○ ongoing			
Alcohol DURING pregnancy					
Smoking DURING pregnancy					
Cocaine__ Crack__ DURING pregnancy					
Marijuana DURING pregnancy					
Other: DURING pregnancy					

ADVICE

Baseline risk explained Yes○ No○ Risk no >1-3% ○

Clinic date:_____ **bring translator ○**

Discussed ○ ultrasound ○ MSAFP ○ triple screen
○ folic acid: amount advised _____

Referred back to MD for suggestion of medications ○

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Infectious Disease

- Chlamydia
- Chicken pox
- CMV
- Genital herpes
- Gonorrhea
- Group B strep
- Coxsackie
- Hepatitis B
- Hepatitis C
- HIV
- Parvovirus B19
- Shingles
- Syphilis
- Varicella

Other: _____

Exposed only
Symptoms? _____

Date of contact with infected person: _____
Date of lesions on contact person: _____

Type of contact:

- blood
- daycare
- fecal
- household
- hospital
- with lesions
- mucosal
- oral
- sexual
- other _____

Patient had disease in the past
Disease clinically diagnosed? No Yes by _____

Referenced advice +box on pg.1

_____
_____
_____

Chemical Exposures

Chemical: _____
Occupation: _____

EXPOSURE
type: direct secondary

where: factory office home school
other _____

route: skin oral inhalation
other _____

duration: minutes hours days
other _____

barrier: gloves mask respirator fumehood
other _____

side effects: nausea vomiting diarrhea rash
headache tremors blurred vision
other _____

Referenced advice + box on pg.1

_____
_____
_____

BREASTFEEDING

Infant Data

Date of birth: _____
Gestational age at birth: _____ wk
Birth weight: _____ kg lb

Are you taking medication as prescribed?
Yes No _____

Number of times breastfed daily: _____
how often? _____

Formulasupplementation? Yes No **Solids?** Yes No
name _____ type _____
age started _____ age started _____
times/day _____ # times/day _____

Referenced advice

_____
_____

ADDITIONAL

_____
_____
_____
_____
_____
_____
_____
_____
_____

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Appendix B: Clinic Form

MOTHERISK PROGRAM

ANTENATAL CLINIC FOR DRUG/CHEMICAL RISK COUNSELLING
THE DIVISION OF CLINICAL PHARMACOLOGY, HOSPITAL FOR SICK CHILDREN, TORONTO, ONTARIO

ID NUMBER: _____

CONSULTATION DATE (d/m/y) _____

CONSULTATION BY: _____

MATERNAL DATA

FULL NAME: _____
Address: _____
_____
Date of birth (dd/mmm/yy) _____
Home Telephone: ( ) _____
Work Telephone: ( ) _____

Biological father's name: _____
Address: same as mother ❑ _____
_____
Date of birth (dd/mmm/yy) _____
Home Telephone: same ❑ ( ) _____
Work Telephone: ( ) _____

Maternal Race: ❑ Caucasian ❑ Black ❑ East Indian ❑ Oriental ❑ Latin American ❑ Other: _____

Marital Status: ❑ Married/Common Law ❑ Single ❑ Divorced ❑ Widowed

Send MR letter to Dr. _____ Dr. _____
Street Address: _____ _____
City/Postal Code: _____ _____

Geographically stable relative: Name: _____ Home telephone: ( ) _____
Relationship to patient: ❑ mother ❑ father ❑ aunt ❑ uncle ❑ cousin ❑ grandparent ❑ sister ❑ brother

OBSTETRICAL HISTORY

gravidity____ parity____ spontaneous abortion <20wks____ fetal death ≥ 20weeks____ therapeutic abortion____
Details on previous pregnancies: _____
_____
_____

Contraception	Method	Start Date	Stop Date	Duration of Use	Pregnancy due to failure?
	❑ none			____d❑ wk❑ mo❑ yr ❑	yes❑ no❑
	❑ abstinence			____d❑ wk❑ mo❑ yr ❑	yes❑ no❑
	❑ rhythm			____d❑ wk❑ mo❑ yr ❑	yes❑ no❑
	❑ condom			____d❑ wk❑ mo❑ yr ❑	yes❑ no❑
	❑ diaphragm			____d❑ wk❑ mo❑ yr ❑	yes❑ no❑
Name of Pill	❑ IUD			____d❑ wk❑ mo❑ yr ❑	yes❑ no❑
_____	❑ oral pill			____d❑ wk❑ mo❑ yr ❑	yes❑ no❑
	❑ spermicide			____d❑ wk❑ mo❑ yr ❑	yes❑ no❑

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PREGNANCY INFORMATION

Last Menstrual Period (d/m/y) _____ **Cycle** every _____ days x ___ days bleeding

Expected Delivery Date (d/m/y) _____ **Current Gestational Age** _____ wk [ ] month [ ]

by : dates [ ] ultrasound [ ]

Pregnancy diagnosed at _____ wks [ ] months [ ] **By which method?** [ ] blood test [ ] urine test [ ] ultrasound

Ultrasounds ? ❑ No ❑ Yes at _____ [ ] wks [ ] months **Results:** [ ] Normal [ ] Other _____

at _____ [ ] wks [ ] months **Results:** [ ] Normal [ ] Other _____

Amniocentesis ? ❑ Yes at _____ [ ] wks [ ] months **Reason:** _____

Results: _____

❑ No Patient has discussed topic with physician already [ ] Yes [ ] No

PRIMARY EXPOSURE INFORMATION

A. Over-the-counter and Prescription Medications OR Radiation

DRUG NAME *or* RADIATION	CALENDAR START DATE	CALENDAR STOP DATE	DRUG DOSE *or* FETAL RAD DOSE	ROUTE	SIDE EFFECTS
1.		[ ] ongoing exposure			
2.		[ ] ongoing exposure			
3.		[ ] ongoing exposure			
4.		[ ] ongoing exposure			
5.		[ ] ongoing exposure			
6.		[ ] ongoing exposure			

Indication for medication	*Prescribing physician*	*Details about medical condition*
1.		
2.		
3.		
4.		
5.		
6.		

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B. Chemical Exposures

Occupation Title: ______________________ ❑ maternal ❑ paternal

CHEMICAL NAME	1.	2.	3.
Where is patient exposed?	home [ ] factory [ ] office [ ] school [ ] studio [ ]	home [ ] factory [ ] office [ ] school [ ] studio [ ]	home [ ] factory [ ] office [ ] school [ ] studio [ ]
Type of exposure *direct use*	[ ]	[ ]	[ ]
in same area when chemical used	[ ]	[ ]	[ ]
Purpose of chemical?			
START DATE of exposure			
STOP DATE of exposure			
For how long?	____ min [ ] hr [ ] days [ ]	____ min [ ] hr [ ] days [ ]	____ min [ ] hr [ ] days [ ]
Per day? week?	day [ ] week [ ]	day [ ] week [ ]	day [ ] week [ ]
Ventilation during exposure?	None [ ]	None [ ]	None [ ]
hood with power exhaust	[ ]	[ ]	[ ]
general - wall & roof fan, ceiling vent	[ ]	[ ]	[ ]
natural - open windows & doors	[ ]	[ ]	[ ]
Barriers during exposure? *gloves*	[ ]	[ ]	[ ]
mask	cartridges yes [ ] no [ ]	cartridges yes [ ] no [ ]	cartridges yes [ ] no [ ]
respirator	[ ]	[ ]	[ ]
apron, helmet, goggles	[ ] ______	[ ] ______	[ ] ______
Can patient smell or taste fumes or vapors during work?	yes [ ] no [ ]	yes [ ] no [ ]	yes [ ] no [ ]
•Can other employees smell or taste fumes or vapors?	yes [ ] no [ ]	yes [ ] no [ ]	yes [ ] no [ ]
Side effects during exposure?	Patient Others	Patient Others	Patient Others
	NONE [ ] [ ]	NONE [ ] [ ]	NONE [ ] [ ]
	diarrhea [ ] [ ]	diarrhea [ ] [ ]	diarrhea [ ] [ ]
	dizziness [ ] [ ]	dizziness [ ] [ ]	dizziness [ ] [ ]
	headache [ ] [ ]	headache [ ] [ ]	headache [ ] [ ]
	nausea /vomit [ ] [ ]	nausea /vomit [ ] [ ]	nausea /vomit [ ] [ ]
	rash [ ] [ ]	rash [ ] [ ]	rash [ ] [ ]
	visual [ ] [ ]	visual [ ] [ ]	visual [ ] [ ]
	other ______	other ______	other ______

C. Herbal Exposure

INGREDIENT	1.	2.
Indication?		
Amount	____ mg [ ] mL [ ] g [ ] % [ ]	____ mg [ ] mL [ ] g [ ] % [ ]
Exposure route	inhale [ ] skin [ ] oral [ ] inject [ ] other [ ]	inhale [ ] skin [ ] oral [ ] inject [ ] other [ ]
Start date		
Stop date		
Side effects during exposure?	NONE [ ] diarrhea [ ] headache [ ] nausea [ ] rash [ ] visual changes [ ] vomiting [ ] OTHER ______	NONE [ ] diarrhea [ ] headache [ ] nausea [ ] rash [ ] visual changes [ ] vomiting [ ] OTHER ______

D. Infectious Disease

AGENT	1.
Date of contact	______
Contact type	direct with lesions [ ] oral [ ] school [ ] resp. secretions [ ] day-care [ ] household [ ] other ______
Date lesions seen on contact person	______
Patient had disease	N [ ] Y [ ] when ______
Method of diagnosis or contact	
Disease diagnosed in patient? •by whom?	N [ ] Y [ ] ______
Patient had relevant vaccinations? date & type	N [ ] Y [ ] ______

Additional Room on page 8

ADDITIONAL MATERNAL EXPOSURES & HISTORY

Ethanol ❑ N ❑Y **wine** *during pregnancy:* _____ glass [ ] bottle [ ] **per** day [ ] week [ ] weekend [ ] month [ ]
beer *during pregnancy:* _____ glass [ ] bottle [ ] **per** day [ ] week [ ] weekend [ ] month [ ]
liquor *during pregnancy:* _____ glass [ ] bottle [ ] **per** day [ ] week [ ] weekend [ ] month [ ]
Date ethanol ingestion stopped _____ when pregnancy diagnosed ❑
additional information _____

Tobacco ❑ N ❑Y *during pregnancy:* _____ cigarettes **per** day [ ] week [ ] weekend [ ] month [ ]
Date tobacco exposure stopped _____ when pregnancy diagnosed ❑
additional information _____

Cocaine ❑ N ❑ Y during pregnancy _____ **per** day [ ] week [ ] weekend [ ] month [ ] _____
Marijuana ❑ N ❑ Y during pregnancy _____ **per** day [ ] week [ ] weekend [ ] month [ ] _____
LSD ❑ N ❑ Y during pregnancy _____ **per** day [ ] week [ ] weekend [ ] month [ ] _____
Date above exposure stopped _____ when pregnancy diagnosed ❑
additional information _____

Anaesthesia during pregnancy? ❑ N ❑Y **type** _____ **date** _____
Radiation during pregnancy? ❑ N ❑ Y **type** _____ **date** _____
type _____ **date** _____

Jacuzzi ❑ N ❑ Y _____ dates of exposure _____
Spas ❑ N ❑ Y _____ dates of exposure _____
Sauna ❑ N ❑ Y _____ dates of exposure _____
Electric blanket ❑ N ❑ Y _____ dates of exposure _____

Occupation description of work _____ ❑ **unemployed**
chemical exposures? complete chart on page 3 ❑ **housewife**
❑ **student**
[ ] high school - grade 9 10 11 12 13
[ ] university - year 1 2 3 4 5 6 7
program _____

Genetic Disease or Malformations ❑ N ❑ Y

Relative of mother	Condition	Relative of biological father	Condition

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PAST MATERNAL MEDICAL HISTORY

Cancer ❑N ❑Y _____
Cardiovascular ❑N ❑Y _____
Central nervous system ❑N ❑Y _____
Diabetes ❑N ❑Y _____
Epilepsy ❑N ❑Y _____
Hematology ❑N ❑Y _____
Hypertension ❑N ❑Y _____
Renal disease ❑N ❑Y _____
Thyroid disease ❑N ❑Y _____
Other _____

BIOLOGICAL FATHER DATA

Occupation description of work _____ ❑ **unemployed**
chemical exposures? complete chart on page 3 ❑ **student**
[ ] high school - grade 9 10 11 12 13
[ ] university - year 1 2 3 4 5 6 7
program _____

DRUG NAME	CALENDAR START DATE	CALENDAR STOP DATE	DOSE	ROUTE	SIDE EFFECTS
1.		[ ] ongoing exposure			
2.		[ ] ongoing exposure			

Indication for medication *More details about medical condition*

1. _____ _____
2. _____ _____

Ethanol ❑N ❑Y **wine** ___ glass [ ] bottle [ ] **per** day [ ] week [ ] weekend [ ] month [ ]
beer ___ glass [ ] bottle [ ] **per** day [ ] week [ ] weekend [ ] month [ ]
liquor ___ glass [ ] bottle [ ] **per** day [ ] week [ ] weekend [ ] month [ ]

Tobacco ❑N ❑Y _____ cigarettes **per** day [ ] week [ ] weekend [ ] month [ ]

Cocaine ❑N ❑Y during pregnancy _____ **per** day [ ] week [ ] weekend [ ] month [ ] _____
Marijuana ❑N ❑Y during pregnancy _____ **per** day [ ] week [ ] weekend [ ] month [ ] _____
LSD ❑N ❑Y during pregnancy _____ **per** day [ ] week [ ] weekend [ ] month [ ] _____

Appendix C: Breast Feeding Follow-Up Form

ID#_____ Follow Up By: _____

Breast Feeding Follow Up Form

Follow Up Date: _____ Consultation Date: _____

MATERNAL DATA

Name: _____
Phone: _____
DOB: _____ G ____ P ____
Weight during BF:_____ lbs / kg
Smoking: _____ cigarettes/ d [ ] w [ ]
Caffeine: _____ cups/day
coffee [ ] tea [ ] soda [ ]

INFANT DATA

Date of Birth: _____
Birth: GA_____weeks Weight_____
Current: Age _____ Weight_____
Twins? Y [ ] N [ ]
Defects: Y [ ] N [ ]
Health Problems: _____

MEDICATIONS

Drug	Dose	Start	Stop	Indication	Stop after M/R?
			ongoing [ ]		Y/N
			ongoing [ ]		Y/N
			ongoing [ ]		Y/N

REASONS FOR STOPPING MEDS

Concerned for baby?Y [ ] N [ ]
No longer needed? Y [ ] N [ ]
Other:_____

STILL BREAST

breast feeds: _____/day (or every _____ hrs)
formula feeds: _____ /day (_____oz. each)
solids: _____ /day (type: _____
Problems with BF? _____

MATERNAL ADVERSE EVENTS

Any maternal problems associated with drug?
N [ ] Y [ ] Specify: _____

NOT EXCLUSIVE BREAST

Age when BF stopped: _____ mos
Age when formula introduced: _____ mos
Age when solids introduced: _____ mos

INFANT ADVERSE EVENTS

Any changes in baby which were concerning?Y [ ] N [ ] GI complaints / Stool Changes / Behavioural
Other: _____

Went to all regular MD visits?Y [ ] N [ ] If no why not: _____

Any extra MD visits or calls?Y [ ] N [ ] GI complaints / Stool Changes / Behavioural
Other: _____

Any visits to the Emergency room?Y [ ] N [ ] GI complaints / Stool Changes / Behavioural
Other: _____

ADVICE: **A** *Safe* **B** *Unsafe* **C** *Unsure* **D** *Other (please elaborate)*

Family MD		Pharmacist	
Ob/Gyn		Prenatal Teacher	
Pediatrician		Other Health Professional	
Gastroenterologist		Family/Friends/Media	

Do we have your permission to contact your child's doctor to confirm the medical details of this event? Y[ ] N[ ]

Child's Doctor: _____

_____ Date Letter Sent: _____

_____

_____

Phone: _____ Response Recieved:

Appendix D: Sample Physician Follow-Up Letter

January 1, 1999

Dr. M. Jones
123 Main Street
Toronto, Ontario
M5G 1X8

Dear Dr. Jones:

Re: Baby's Name DOB: January 1, 1997

On January 1, 1998, your patient's mother was counselled by the Motherisk Program at the Hospital for Sick Children regarding the safety of Asacol® while breastfeeding. During a telephone interview to ascertain the child's health status, we were given verbal consent to contact you to corroborate the medical details of the following event:

one incident of blood and mucus in the stool shortly after birth

If available, would you send us a copy of the medical examination or details of the consultation pertaining to this event?

Thank you for your anticipated cooperation.

Sincerely,

Myla Moretti, BSc.
Division of Clinical Pharmacology

Gideon Koren, MD, ABMT, FRCP(C)
Director, Motherisk Program

Appendix E: List of Publications and Reprints

Publications

Loebstein R, Addis A, Ho E, Andreou R, Sage S, Donnenfeld AE, Schick B, Bonati M, Moretti ME, Lalkin A, Pastuszak A, Koren G. Pregnancy outcome following gestational exposure to fluoroquinolones: a Multicenter Prospective Controlled Study. Antimicrobial Agents and Chemotherapy 1998;42:1336-1339.

Moretti ME. Medication use during pregnancy: fetal risk versus maternal benefit? Corridor Consultations, Patient care 1998;9:12-14.

Ito S, Moretti M, Liau M, Koren G. Initiation and duration of breast-feeding in women receiving antiepileptics. American Journal of Obstetrics and Gynecology 1995;172:881

Moretti ME, Ito S, Koren G. Disposition of maternal ketoconazole in breast milk. American Journal of Obstetrics and Gynecology 1995;173:1625-1626.

Moretti M. Drugs usually contraindicated while breastfeeding. Motherisk Newsletter 1994;3:3-4.

Moretti ME, Ito S, Koren G. Drugs During Breastfeeding: Rationale Based Contraindications. In: Bailliere's Clinical Paediatrics, Paediatric Pharmacology - towards evidence based drug therapy, Diav-Citrin O, Koren G, eds. (*in press*)

Moretti ME, Koren G. Motherisk I. In: Maternal-Fetal Toxicology, 3rd edition. G Koren ed. *(Submitted).*

Meetings

Podium Presentations

Moretti ME, Ito S, Koren G. Therapeutic drug monitoring in the lactating patient. Paper presented at the 8th International Conference of The Organization of Teratology Information Services (OTIS), June 22-25, 1995; San Diego, California.

Moretti ME, Loebstein R, Addis A, Ho E, Andreou R, Sage S, Donnenfeld AE, Schick B, Bonati M, Lalkin A, Pastuszak A, Koren G. Pregnancy outcome following gestational exposure to fluoroquinolones: a Multicenter Prospective Controlled Study Paper presented at: Annual meeting of the European Network of Teratology Information Services (ENTIS); March, 1998; Rome, Italy.

Poster Presentations

Moretti ME, Chong D, Ito S, Koren G. Incidence of breastfeeding among women on chronic anti-thyroid therapy. Paper presented at the 8th International Conference of The Organization of Teratology Information Services (OTIS), June 22-25, 1995; San Diego, California.

Moretti ME, Liau-Chu M, Taddio A, Ito S, Koren G. Adverse Events in breastfed infants exposed to anti-histamines in maternal milk. Paper presented at the 8th International Conference of The Organization of Teratology Information Services (OTIS), June 22-25, 1995; San Diego, California.

Moretti ME, Ito S, Koren G. Validation of a predictive model of drug excretion into human milk. (Abs.) Presented at the 66th Annual Meeting of the Royal College of Physicians and Surgeons of Canada, September 25-28, 1997; Vancouver, Canada.

Reproduced from Moretti M. Drugs Usually Contraindicated While Breastfeeding. Motherisk Newsletter 1994;3:3-4 with permission from the Motherisk Program, Toronto, Canada.

Drugs Usually Contraindicated While Breast-Feeding

Though many drugs are quite safe for a mother to take while nursing her child there are several agents for which safety during breast-feeding is not well-defined and may be a risk to the infant. Drugs which are contraindicated or should be used with caution in lactating women are described here.

Antineoplastics and Immune Suppressants

Even if small amounts of the drug were to be excreted

into milk, the inherently toxic nature of these medications warrants caution with their use.

Ergot Alkaloids

Due to the dopaminergic activity of the ergot alkaloids they may have the ability to suppress prolactin and hence lactation. If breast-feeding is to be considered, milk volume must be monitored in mothers. Bromocriptine is used therapeutically to prevent lactation and is therefore contraindicated in nursing mothers. Short term, low dose therapy with ergonovine and methylergonovine does not cause a risk to the infant. However, methylergonovine would be the preferred choice of the two because it does not have prolactin lowering tendencies. Ergotamine is also able to affect milk secretion and is not a preferred choice while nursing because of the risk of ergotism in the infant. Signs of toxicity in the infant may include vomiting, weight loss and weak pulse.

Gold

Infants should be closely monitored if breast-fed during maternal gold therapy as the exact effect on infants is not known at this time. Reported milk levels vary widely and aurothiomalite has been measured in both urine and plasma of infants.

Iodine

Iodine containing compounds are not generally recommended during breast-feeding. Iodine readily gains access to breast milk and can lead to hypothyroidism in the infant.

Lithium Carbonate

Breast-feeding during maternal lithium therapy is generally thought to be contraindicated because lithium has been found to attain concentrations in the milk of up to 40% of the maternal weight adjusted dose. Moreover, the excretion of lithium in milk appears to vary a great deal among patients. Since some women will have relatively low excretion of lithium into their milk and breast-feeding can be extremely beneficial to a manic depressive mother, it seems quite reasonable to initiate breast-feeding. It is recommended that infants' serum lithium concentrations be monitored and the infant be observed for signs of toxicity. Breast-feeding may be continued as long as infants' blood levels remain well below therapeutic concentrations and the infant shows no signs of toxicity.

Radiopharmaceuticals

Radioactive materials are contraindicated while breast-feeding, in order to avoid excess infant exposure to radioactivity. Once radioactivity is cleared from the mother's body however, breast-feeding can be resumed. The length of time of breast-feeding interruption will vary with each radioisotope used depending on radioactive decay and elimination by the mother. Motherisk can be consulted regarding this length of time.

Social Drugs and Drugs of Abuse

Alcohol freely distributes into milk and will be ingested by nursing infants. Moderate, occasional alcohol consumption is not likely to pose a problem to the infant, but heavy alcohol consumption is to be avoided. Ideally, nursing should be withheld temporarily after alcohol consumption; at least one hour per drink to avoid unnecessary infant exposure. Side effects reported in infants include sedation and impairment of motor skills. Both alcoholic and non-alcoholic beer increase prolactin secretion.

Cigarette smoking is not recommended in nursing mothers. Nicotine and its major metabolite are detectable in milk. Smoking should be avoided while breast-feeding because it has been associated with infantile colic, lowered maternal prolactin levels and consequently, earlier weaning.

Street drugs can be very potent. Even very small amounts can have pharmacological activity and adverse effects on the infant. It is suggested that breast-feeding be at least temporarily delayed after maternal use of these agents and caution should be used to avoid infant exposure to smoke fumes. Infants may experience toxicity after maternal cocaine use, and marijuana use has been associated with slower motor development at one year of age.

Myla Moretti, Motherisk

Disposition of maternal ketoconazole in breast milk

Myla E. Moretti, BSc, Shinya Ito, MD, and Gideon Koren, MD
Toronto, Ontario, Canada

Infant exposure to ketoconazole in human milk was calculated to be 0.4% on average (maximum 1.4%) of those expected from therapeutic doses given directly to infants. Potential risks of adverse reactions from this low exposure level seem to be outweighed by the benefits of breast-feeding. (Am J Obstet Gynecol 1995;173:1625-6.)

Key words: Ketoconazole, breast-feeding, human milk, breast milk

Ketoconazole, an imidazole compound used orally or topically to treat fungal infections, is a weak basic compound with lipophilic characteristics. Although these factors suggest high excretion of the drug in milk, its extensive plasma protein binding (99%) implies otherwise; the higher the protein binding, the slower the drug diffusion into milk. However, no data are available on ketoconazole excretion into human milk.

In this report we describe what we believe is the first account of ketoconazole measurement in human milk after maternal dosing.

Case report

A 41-year-old woman (weight 82 kg) who was breast-feeding a 1-month-old child was prescribed ketoconazole in doses of 200 mg once a day (2.4 mg/kg) for 10 days to treat a fungal infection. On day 5 of the 10-day course she contacted us, asking information on safety of breast-feeding during maternal ketoconazole therapy, although she noticed no adverse reactions either in herself or in the baby. After the adverse drug reaction profile of ketoconazole and lack of information on its excretion into human milk were explained to the patient and contrasted with the potential benefits of breast-feeding, she decided to complete the treatment course and asked us to estimate infant exposure to the drug by measuring ketoconazole concentrations in her milk.

Manually expressed milk samples were collected 1.75, 3.25, 6.0, 8.0, and 24 hours after the tenth dose. The samples were stored at −20° C until analysis by high-performance liquid chromatography by the Janssen Research Foundation (Beerse, Belgium). The coefficient of variation was 2.6%, and the detection limit was 0.005 μg/ml; concentrations lower than the detection limit were regarded as 0.004 μg/ml in later analysis.

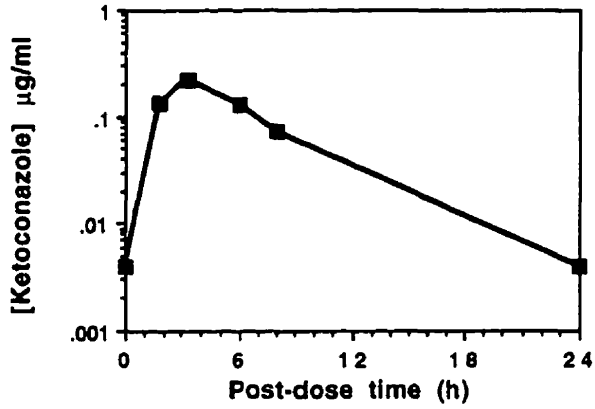

Fig. 1. Concentration-time profile of ketoconazole in human milk. Breast-feeding woman received 2.4 mg/kg/day of oral ketoconazole for 10 days. Milk samples were collected after tenth dose. Peak concentration of 0.22 μg/ml was observed at 3.25 hours postdose. Average concentration was 0.068 μg/ml; average infant exposure was estimated to be 0.4% of mother's dose on weight basis. Note that sample at time 24 hours was lower than detection limit and was assumed to be 0.004 μg/ml. Concentration at time 0 hours was assumed to be same as that at time 24 hours.

The area under the curve of ketoconazole concentrations in milk from time 0 to 24 hours of the dose was calculated by use of a trapezoidal method on the assumption of steady state. This assumption appears valid because the ketoconazole concentration in the plasma reaches 97% of steady state (five elimination half-lives) by the third dose when given every 24 hours (an average terminal elimination half-life of ketoconazole is 8 hours: 8 hours × 5 = 40 hours).

The mean concentration of ketoconazole in milk ($C_{milk,av}$) was calculated as follows: $C_{milk,av} = AUC_m/24$ hours, where AUC_m is the area under the curve of ketoconazole concentrations in milk. By multiplying the mean concentration with an assumed infant's milk intake of 150 ml/kg/day, an infant daily dose of ketoconazole through breast-feeding was estimated. Similarly, a maximum infant daily dose based on the highest drug concentration in milk was calculated.

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The highest concentration of ketoconazole in milk (0.22 μg/ml) was observed at postdose time 3.25 hours. At postdose time 24 hours ketoconazole was undetectable (Fig. 1). Assuming that concentrations at postdose times 0 and 24 hours were 0.004 μg/ml, the area under the curve and the mean concentration were calculated to be 1.62 hours · μg/ml and 0.068 μg/ml, respectively. Hence a daily ketoconazole dose the exclusively breast-fed infant would ingest is 0.01 mg/kg per day (0.068 μg/ml × 150 ml/kg per day), which is about 0.4% of the mother's weight-adjusted dose (2.4 mg/kg per day). Similarly, a maximum ketoconazole dose the infant would receive through breast-feeding is 0.033 mg/kg per day (0.22 μg/ml × 150 ml/kg per day), corresponding to about 1.4% of the mother's dose.

Comment

The exposure of the infant to drugs in breast milk can be theoretically estimated from a value of drug clearance and a predicted ratio of milk–to–maternal plasma drug concentrations. The details were described elsewhere.[1] Briefly, when the exposure level of the infant to the drug in milk is expressed as percentage of the mother's dose on a weight basis, the following equation holds: Infant exposure (%) = 10 × MP ratio/CL, where MP ratio is the ratio of milk–to–maternal plasma drug concentrations and CL is an average infant's total body clearance of drug (milliliters per kilogram per minute), and the daily milk intake of the infant is assumed to be 150 ml/kg.[1] For example, an infant exposure of 100% indicates that the dose of drug the infant would be ingesting through breast milk is the same as the mother's dose per body weight. It is now possible to roughly predict the milk–to–maternal plasma ratio from physicochemical characteristics of drug.[2] Also, a representative population value of clearance of drug is usually known and reported in standard reference articles. Therefore, even if there is no study reporting measured drug concentrations in breast milk, the infant exposure level can be estimated.

Given information on the physicochemical characteristics of ketoconazole,* its average milk–to–maternal plasma ratio can be predicted to be 0.38 according to a formula proposed by Begg et al.[2] Because the reported average of oral clearance of ketoconazole is 8.4 ml/kg per minute, the infant exposure is calculated as follows by use of the equation shown previously (Infant exposure [%] = 10 × MP ratio/CL): 10 × 0.38/8.4 = 0.45%. In this patient report the average infant exposure calculated from the measured drug concentrations in milk was 0.4% of the maternal therapeutic doses on a weight basis, consistent with the above prediction. Even if the infant was breast-fed constantly at the time that the drug concentration was at its highest level in milk, maximum exposure is estimated to have been 1.4% of the mother's dose per body weight. Assuming that an infant therapeutic dose is in the same range as those for adults on a weight basis, the exposures of infants to ketoconazole through breast milk are considered to be minimal. Infant exposure to drugs in milk measuring < 10% of those expected from therapeutic doses directly given to the infant is generally considered acceptable in breast-feeding for a healthy term infant so far as dose-related short-term effects are concerned.

The most common side effects of ketoconazole are dose-dependent nausea and vomiting. Skin rash, pruritus, abdominal pain, hepatic dysfunction, and changes in endogenous steroid disposition may also be seen in some patients who receive therapeutic doses of the drug. Although more data are clearly needed, our results suggest that maternal monotherapy with ketoconazole may be compatible with breast-feeding.

We thank Janssen Pharmaceutica, Beerse, Belgium, for their analysis of the milk samples.

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*Plasma protein binding: 99%; lipophilicity: log (O/W) = 3.73 at pH 11.8; and ionization characteristics: pKa = 6.5 and 2.9 (Janssen Pharmaceutica Inc. Personal communication), where O/W is an octanol-to-water partition coefficient of ketoconazole. When used for the calculation, pKa of 6.5 was used, and log (O/W) was transformed to 3.65 at pH 7.2 according to a standard formula.

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Initiation and duration of breast-feeding in women receiving antiepileptics

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OBJECTIVE: Our purpose was to characterize breast-feeding initiation and the duration of breast-feeding in women receiving antiepileptics.
STUDY DESIGN: A cohort study was performed on 34 pregnant epileptic women receiving antiepileptics and 34 pregnant age-matched controls.
RESULTS: Fifty percent of the group receiving antiepileptics chose breast-feeding as the initial feeding method, which was significantly less than the controls (85%, $p = 0.004$). The decision to choose initial feeding methods was closely associated with advice from physicians and other sources. The 17 women in the antiepileptics group who chose breast-feeding initially terminated breast-feeding significantly earlier than did the control group (4.7 ± 2.6 vs 9.3 ± 5.7 months post partum, $p < 0.005$).
CONCLUSIONS: Mothers receiving antiepileptics tend to choose formula feeding. Even when they choose breast-feeding initially, its duration is shorter than usual. Consensus and guidelines on this matter among experts remain to be reflected on and effectively implemented in current medical practice. (Am J Obstet Gynecol 1995;172:881-6.)

Key words: Breast-feeding, drug, maternal medication, antiepileptics, adverse effects

Although any pharmacotherapy is accompanied with risks of adverse reactions, the benefits of the treatment are expected to outweigh them. A unique situation arises when a patient is breast-feeding. The risks to innocent bystanders (i.e., breast-fed infants) posed by drugs in breast milk have to be taken into account along with the benefits of breast-feeding. This enforces difficult decision making on nursing women and their physicians. As a result, short-term or symptomatic drug treatment may be avoided to circumvent these difficulties. However, the situation becomes more complicated when mothers need long-term therapy, because they have usually no choice but to continue the medications. Maternal antiepileptic therapy is a typical example.

Several first-line antiepileptics such as carbamazepine, phenytoin, and valproic acid have been classified as usually compatible with breast-feeding.[1] Although

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there are reports of adverse reactions in infants associated with maternal use of some of the antiepileptic drugs,[1, 2] an attempt to initiate breast-feeding is justified if the infant's well-being is adequately monitored. Even during maternal therapy with phenobarbital, which might result in therapeutic serum concentrations in the breast-fed infants,[1, 2] initiation of breast-feeding is warranted, with close monitoring of the infant's conditions.

The view in favor of breast-feeding during maternal antiepileptic therapy seems rational, considering the ever-increasing evidence of benefits of breast-feeding for the suckling infant.[3, 4] However, little is known about how epileptic mothers are instructed and which infant feeding methods they actually choose. These data should serve for effective implementation of patient education and for updating clinicians about this issue.

In this study we quantify the incidence of breast-feeding initiation of women on long-term anticonvulsant therapy, the factors underlying their choices of infant feeding methods, and the duration of the breast-feeding.

Material and methods

Study setting. The Motherisk program is a teratogen-toxicant information service during pregnancy and lactation, whose scope encompasses not only drugs and chemicals but also radiation and infectious agents.[5, 6] Women with concerns about effects of their medications or of any kind of maternal exposure on the fetus or breast-fed infant telephone the program with or without referral by health professionals such as physicians, pharmacists, and nurses. Their questions are answered over the phone by trained counselors or physicians after demographic and medical information is obtained. Women receiving long-term drug therapy such as antiepileptics are subsequently seen in the clinic to be counseled in detail. One of the unique features of this program is that all cases undergo follow-up interviews to record the outcome of pregnancy (the Motherisk cohort) or of breast-feeding (the Motherisk breast-feeding cohort).[6]

Subjects. From January 1990 to December 1992, 70 women receiving antiepileptics who were pregnant or planning pregnancy were referred to the Motherisk clinic by their physicians for detailed information on fetal effects of antiepileptics. Between April and June 1993 we conducted interviews with those women. Of these 70, 13 did not become pregnant, 10 were lost to follow-up, six were still pregnant, four had spontaneous or therapeutic abortions, two declined to participate, and one was delivered of a preterm baby. The remaining 34 women were included in the analysis. In addition, we interviewed 34 age-matched controls (± 1 year) identified from the Motherisk cohort who were seen during the same month, as were their counterparts, and who were receiving neither antiepileptics including tranquilizers nor any known teratogenic substances.

Data collection. Information regarding the following characteristics was confirmed or newly obtained during the interviews: maternal drug treatment during and after pregnancy, initial choice of feeding method, sources and nature of advise on feeding methods, duration of breast-feeding, and demographic data such as annual family income, maternal and paternal education, and marital status. They were also asked whether the infants were diagnosed with any adverse effects such as withdrawal syndromes and toxic symptoms from the drugs in breast milk.

The women were questioned in an open-ended manner as to why they initially chose to breast- or formula-feeding (first responses). Subsequently, closed-ended questions for specific reasons were asked (subsequent responses). The women were allowed to list multiple reasons for both the open- and closed-ended questions.

The sources of information on feeding methods were identified by asking whether they received information or advice from a general practitioner, a pediatrician, an obstetrician or gynecologist, a neurologist, a pharmacist, a public health nurse, the Motherisk clinic, family members, friends, lay media, and others.

Data analysis. The information or advice epileptic women received were categorized into three groups according to the maternal reports: recommending breast-feeding, recommending formula feeding, and equivocal. To quantify the overall trend of the advice, a cumulative advice score was computed for each woman by summing up a number assigned to each category of advice: +1 for advice recommending breast-feeding, −1 for advice recommending formula feeding, and 0 for equivocal advice. (For example, if a woman received advice from three sources recommending breast-feeding and one recommending formula feeding, the cumulative advice score would be +2. If a woman received conflicting advice from two sources and one equivocal advice, the cumulative advice score would be 0. If she received advice from three sources recommending formula feeding, the score would be −3.)

Results between two groups (antiepileptics vs control and breast-feeding vs formula feeding) were compared with unpaired Student t test (two-tailed) or χ^2 analyses with continuity correction where appropriate; the unpaired t test was used because the controls were matched only for age (for convenience) in spite of possible other factors associated with maternal choices of feeding methods. Data are expressed as means ± SD, unless otherwise stated. The Mann-Whitney U test was used to compare the cumulative advice scores between the epileptic women who chose breast-feeding and

Table I. Demographic characteristics and feeding methods of patients

	Antiepileptics group (n = 34)	*Control (n = 34)*	*Significance*
Infant's gestational age (mo)	39.5 ± 1.4	39.7 ± 1.5	$p = 0.6$
Maternal age (yr)	27.2 ± 4.5	27.6 ± 3.1	$p = 0.6$
Parity			
1	22	24	$p = 0.8$
2	12	10	
Marital status			
Married	32	30	$p = 0.7$
Single	2	4	
Family income per year			
< C$20,000	3	4	$p = 0.9$
C$21-40,000	8	7	
C$41-60,000	15	12	
> C$60,000	7	8	
Maternal education			
≤ 13 yr	15	13	$p = 0.6$
> 13 yr	19	21	
Paternal education			
≤ 13 yr	12	7	$p = 0.4$
> 13 yr	21	24	
Initial feeding methods			
Breast-feeding	17	29	$p = 0.004$
Formula feeding	17	5	
Duration of breast-feeding (mo)	4.7 ± 2.6 ($n = 17$)	9.3 ± 5.7 ($n = 29$)	$p < 0.005$

those who chose formula feeding and the duration of breast-feeding between the antiepileptic group and the controls.

Results

Initiation and duration of breast-feeding. Of the 34 women in the antiepileptic group, 30 received monotherapy: 19 carbamazepine, four phenytoin, four valproic acid, two phenobarbital, and one ethosuximide. The remaining four underwent polytherapy: one valproic acid + phenobarbital, one valproic acid + clobazam, one phenytoin + valproic acid, and one carbamazepine + valproic acid.

All infants in the control group and in the antiepileptic group were born at term and had uneventful perinatal and postnatal courses. The demographic characteristics were similar between the antiepileptic and control groups (Table I). By contrast, only 50% (17/34) of the women receiving antiepileptics initiated breast-feeding, compared with 85% (29/34) in the control group (Table I, $p = 0.004$). Furthermore, the duration of breast-feeding was significantly shorter in the antiepileptics group (median 5 months) than in the control group (median 7.0 months, $p < 0.005$, Table I). A total of 65% (11/17) in the antiepileptics group terminated breast-feeding by 6 months post partum, whereas so did 21% (six of 29) in the control group ($p = 0.008$).

When the analysis was confined to women receiving monotherapy with carbamaezpine, phenytoin, or valproic acid, which are considered to be at the safest end of the spectrum for breast-feeding compatibility of antiepileptics, a similar trend was observed: the initiation rate and duration of breast-feeding were 59% (16/27) and 4.8 ± 2.6 months (median 5 months), respectively, which were significantly lower and shorter than those of the control ($p = 0.045$ for initiation rate and $p < 0.005$ for duration).

No adverse reaction (withdrawal or toxic effects) attributable to the maternal antiepileptic drugs was reported by the mothers for any of the infants in this series.

Subgroup analysis in the antiepileptics group (breast-feeding vs formula feeding group). There were no demographic differences between the breast-feeding and formula-feeding subgroups (Table II). Of the 34 epileptic women, 32 (16 breast-feeding, 16 formula feeding) reported that they obtained information about compatibility of the drugs with breast-feeding from third parties. The sources of information for the 32 patients are summarized in Table III; 45% were from physicians. The cumulative advice scores in the breast-feeding and formula-feeding subgroups were +4.3 (95% confidence interval +3.0 to +5.6) and −1.1 (95% confidence interval −2.7 to +0.5), respectively ($p < 0.001$, Table II). The women in the breast-feeding group obtained the information from more sources (5.0 ± 2.3 per patient) than did those in the formula group (3.2 ± 2.4 per patient, $p = 0.03$).

Thirty women receiving antiepileptics (15 breast-feeding and 15 formula feeding) received advice from a total of 56 physicians. Because four physicians were

Table II. Subgroup analysis of women receiving antiepileptics

Feeding methods	*Breast-feeding (n = 17)*	*Formula feeding (n = 17)*	*Significance*
Infant's gestational age (mo)	39.3 ± 1.2	39.7 ± 1.7	$p = 0.4$
Maternal age (yr)	27.3 ± 4.1	27.1 ± 4.9	$p = 0.9$
Parity			
1	11	11	$p = 1.0$
2	6	6	
Marital status			
Married	17	16	$p > 0.9$
Single	0	1	
Family income per year			
< C$20,000	2	1	$p = 0.2$
C$21-40,000	2	6	
C$41-60,000	10	5	
> C$60,000	2	5	
Maternal education			
≤ 13 yr	7	8	$p > 0.9$
> 13 yr	10	9	
Paternal education			
≤ 13 yr	5	7	$p = 0.6$
> 13 yr	12	9	
Mean cumulative advice scores ($n = 16$)			
Mean and 95% confidence interval	+4.3 (+3.0-+5.6)	−1.1 (−2.7-+0.5)	$p < 0.001$
Mean cumulative advice scores from physicians ($n = 15$)			
Mean and 95% confidence interval	+1.7 (+1.0-+2.5)	−0.9 (−1.7-−0.01)	$p < 0.001$

Table III. Patient sources of information on compatibility of drugs with breast-feeding

Sources	*No.*
Physicians	64 (45%)
Motherisk	19 (13%)
Family members	16 (11%)
Friends	16 (11%)
Public health nurse	11 (8%)
Lay media	11 (8%)
Pharmacist	2 (1%)
Others	3 (2%)
TOTAL	142 (100%)

shared by two patients and one physician was shared by five patients, overall there were 64 instances of physician advice. The patients reported that, of these 64, 18 sources (28%) were against breast-feeding during therapy, 30 (47%) were in favor of breast-feeding, and 16 (35%) were equivocal. The cumulative scores of the physician advice were +1.7 (95% confidence interval +1.0 to +2.5) in the breast-feeding women and −0.9 (−1.7 to −0.01) in the formula-feeding women ($p < 0.001$, Table II). The numbers of physicians as an information source were not significantly different between the two groups (2.1 ± 1.3 per patient in the breast-feeding group and 1.8 ± 1.1 per patient in the formula feeding group, $p = 0.06$).

Of these 30 women, 23 (14 breast-feeding, nine formula feeding) were receiving monotherapy with carbamazepine, phenytoin, or valproic acid. There were 49 instances of physician advice from 46 physicians for the 23 women (one physician was shared by two patients and another was shared by three patients). Of these 49, 10 (20%) were against breast-feeding during the therapy, 29 (59%) were in favor of breast-feeding, and 10 (20%) were equivocal. The cumulative advice scores were +1.9 (+1.1 to +2.7) in the breast-feeding women and −0.5 (−1.5 to +0.5) in the formula-feeding women ($p < 0.001$). The numbers of physician advice per patient were 2.1 ± 1.3 in the breast-feeding group and 1.5 ± 1.0 in the formula feeding group ($p = 0.2$).

Reasons for the choices of feeding methods. In the 17 epileptic women who chose formula feeding, the first responses for their choice of infant's feeding methods concentrated on "maternal medication" (11, 65%). When first and subsequent responses are combined, the two most cited reasons in these 17 women who chose formula feeding were "maternal medication" (15, 88%), and "maternal illness" (eight, 47%).

In the 17 women who breast-fed their infants during antiepileptic therapy, the most frequent first response as to why they chose breast-feeding was "for the infant's health in general" (12, 71%). When first and subsequent responses are combined, the two most cited reasons for breast-feeding were "for the infant's health in general" (15, 88%), and "better mother-infant bonding" (15, 88%).

In the control group the two most cited reasons (first and subsequent responses combined) for breast-feeding were "better mother-infant bonding" (29, 100%) and "immunologic advantages" (29, 100%). In five women who chose formula feeding the two most cited reasons

for formula feeding (first and subsequent reasons combined) were "previous experiences" (three, 60%) and "most convenient" (two, 40%).

Comment

Our data confirm the clinical impression that the incidence of breast-feeding initiation of women receiving antiepileptics is low. The incidence of breast-feeding initiation in controls in this study (85%) is similar to that reported in a Toronto population in the mid-1980s.[7] Confined to carbamazepine, valproic acid, and phenytoin, which are at the safest end of the spectrum of breast-feeding compatibility of antiepileptics, our results show a similar trend: the incidence of breast-feeding initiation is still substantially lower than that in controls. Because important demographic factors (e.g., socioeconomic status, maternal age, marital status, and educational levels) for the choice of breast-feeding[8] were similar between the two groups, the difference may be ascribed to the maternal drug therapy or to the disease itself. Indeed, "maternal medication" and "maternal illness" were the two most frequently cited reasons for the choice of formula feeding among women receiving anticonvulsants.

We found that these women terminated breast-feeding earlier than did the controls. The study design did not allow us to separate effects of the drugs from those of the disease itself on the duration of breast-feeding. Reasons underlying the decision to wean infants and to terminate breast-feeding earlier than usual are unknown. Adverse effects on infants could not be the cause, because none was reported in this series.

Most antiepileptic drugs are generally considered compatible with breast-feeding.[1] For example, an estimated maximal dose of carbamazepine that the breast-fed infant would ingest in breast milk is 3% to 5% of the weight-adjusted maternal dose. Namely, the infant exposure level would be only 3% to 5% of the infant's therapeutic exposure. Similar figures were obtained with other drugs such as phenytoin and valproic acid.[9, 10] The view in favor of breast-feeding during maternal antiepileptic therapy is further supported by the consensus guidelines among neurologists, which state that taking antiepileptic drugs (except for sedative ones such as phenobarbital, primidone, or benzodiazepines) does not constitute a contraindication for breast-feeding.[11] Although monitoring the infant's health is important to detect idiosyncratic reactions or any dose-related effects, the risk of these reactions seems to be outweighed by the benefits of breast-feeding, apparent even in the industrialized countries.[3] Therefore a rational approach for potential lactating women receiving antiepileptics who have term healthy neonates would be to start breast-feeding while monitoring the infant's health, which might include a regular visit to a pediatrician. Regular visits to monitor the infant's condition may necessitate an unaffordable extra effort for parents. In this case, a conservative approach[10] may be taken, which classifies phenobarbital and ethosuximide as "to be avoided."

In spite of the current understanding described above, our results showed that 41% of physician advice was perceived by the women as either against breast-feeding or equivocal even when the analysis was confined to carbamazepine, phenytoin, and valproic acid. Consensus and guidelines among experts[1, 2, 9-11] remain to be effectively implemented in current medical practice.

The information and advice the epileptic women received regarding the drugs and breast-feeding were closely associated with their decision as to which feeding method to choose. When separately analyzed as the most influential advice, advice from physicians showed a similar close association with the women's choices of feeding methods. Although association between physician advice and the mother's choice of feeding methods has been suggested in this study, causation could not be examined by means of the cohort study design. In addition, because our results were based on maternal reports, the findings might have reflected what the women believed or were willing to report to us rather than what the physicians actually attempted to convey. Whether educational intervention by health professionals affects women's decisions on infant feeding methods awaits further studies. In the mean time, more discussion about benefits of breast-feeding, which usually outweigh risks posed by the maternal antiepileptic drugs, is warranted in the medical community.

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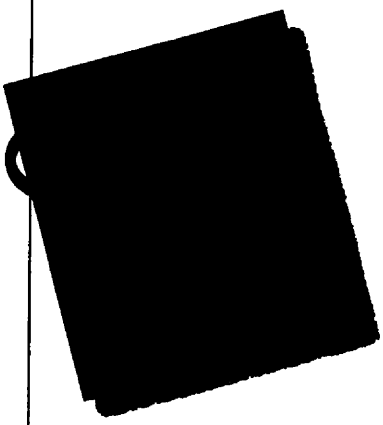

Medication use during pregnancy: Fetal risk versus maternal benefit?

Q I am frequently asked about OTC drugs that are safe to use in pregnancy. Could you please provide a list of both OTC and prescription drugs acceptable in pregnancy?
Jacqueline H. Hurst, MD
Vancouver

A While most patients are extremely hesitant to take medications during pregnancy, there are actually very few drugs which are currently known to be harmful to the developing fetus. Clearly when considering treat-

Allergy, cough, and cold	
antihistamines	brompheniramine
	chlorpheniramine
	dexbrompheniramine
	diphenhydramine
	pheniramine
	pyrilamine
cough suppressants	dextromethorphan
decongestants	phenylephrine
	pseudoephedrine
expectorants	guaifenesin
lozenges or throat sprays	benzocaine
	camphor
	menthol
nasal sprays	oxymetazoline
	xylometazoline
Constipation	
bulk-forming agents	
stool softeners/osmotic agents	
Heartburn, dyspepsia, and flatulence	
alginic acid	
antacids	aluminum hydroxide
	calcium carbonate
	magnesium hydroxide
	sodium bicarbonate+
bismuth salicylate*	
kaolin and pectin	
simethicone	
Infectious agents	
clotrimazole (topical)	
miconazole (topical)	
Pain and fever	
acetaminophen	
ASA*	
ibuprofen*	

*NSAIDs and salicylates should be used with caution in the third trimester due to concerns of excessive maternal bleeding and premature closure of the ductus arteriosus
+ excessive use of bicarbonate may lead to maternal metabolic alkalosis

Asthma
inhaled steroids
inhaled ß-adrenergic agonists

Cardiovascular
anticoagulants
heparin
antihypertensives
α-methyldopa (Aldomet)
hydralazine (Apresoline)
ß-blockers†
digoxin (Lanoxin)

Depression
tricyclic antidepressants°
fluoxetine (Prozac)

Diabetes
insulin

Gastrointestinal disease
5-aminosalicylic acid (e.g., Asacol, Mesasal, etc.)
sulfasalazine (Salazopyrin)

Infections
cephalosporins
clindamycin (Dalacin C)
erythromycin (e.g., Eryc, Erythromid, etc.)
nitrofurantoin (Macrodantin, Macro BID)
penicillins

Nausea and vomiting
pyridoxine/doxylamine (Diclectin)

Pain, fever and inflammation
NSAIDs*
acetaminophen
codeine§
morphine§
meperidine§ (Demerol)

Psychoses
haloperidol (Haldol)
phenothiazines‡

Thyroid disease
levothyroxine (Eltroxin, Synthroid)
liothyronine (Cytomel)

† observe for IUGR and signs of ß-blockade in neonate
° tricylic antidepressants may cause neonatal withdrawal symptoms
* NSAIDs and salicylates should be used with caution in the third trimester due to concerns of maternal bleeding and premature closure of the ductus arteriosus
§ opioids may lead to addiction and/or withdrawal in the neonate if used near term
‡ third-trimester use of phenothiazines is associated with extrapyramidal symptoms in infant

ment for a pregnant patient, the risks to the fetus need to be outweighed by the benefits of providing adequate treatment to the mother. Patients and their healthcare providers should first consider whether the medication they are about to take is necessary. The following tables provide a list of both OTC and prescription drugs for which there is sufficient information to suggest there is no increased teratogenic risk to the developing fetus, with a few caveats indicated. Absence from this list, however, does not necessarily imply teratogenic potential.

The Motherisk Program at The Hospital for Sick Children in Toronto (416-813-6780) provides consultation to patients and healthcare providers regarding the risks of exposures in pregnancy.

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Pregnancy Outcome Following Gestational Exposure to Fluoroquinolones: a Multicenter Prospective Controlled Study

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Concerns regarding the teratogenicity of fluoroquinolones have resulted in their restricted use during gestation. This is despite an increasing need for their use due to emerging bacterial resistance. The objectives of the present investigation were to evaluate pregnancy and fetal outcomes following maternal exposure to fluoroquinolones and to examine whether in utero exposure to quinolones is associated with clinically significant musculoskeletal dysfunctions. We prospectively enrolled and followed up 200 women exposed to fluoroquinolones (norfloxacin, ciprofloxacin, ofloxacin) during gestation. Pregnancy outcome was compared with that for 200 controls matched for age and for smoking and alcohol consumption habits. Controls were exposed to nonteratogenic, nonembryotoxic antimicrobial agents matched by indication, duration of therapy (±3 days), and trimester of exposure. Rates of major congenital malformations did not differ between the group exposed to quinolones in the first trimester (2.2%) and the control group (2.6%) (relative risk, 0.85; 95% confidence interval, 0.21 to 3.49). Women treated with quinolones had a tendency for an increased rate of therapeutic abortions compared with the rate among women exposed to nonteratogens (relative risk, 4.50; 95% confidence interval, 0.98 to 20.57), resulting in lower live-birth rates (86 versus 94%; $P = 0.02$). The rates of spontaneous abortions, fetal distress, and prematurity and the birth weight did not differ between the groups. Gross motor developmental milestone achievements did not differ between the children of the mothers in the two groups. We concluded that the use of fluoroquinolones during embryogenesis is not associated with an increased risk of major malformations. There were no clinically significant musculoskeletal dysfunctions in children exposed to fluoroquinolones in utero. The higher rate of therapeutic abortions observed in quinolone-exposed women compared to that for their controls may be secondary to the misperception of a major risk related to quinolone use during pregnancy.

Fluoroquinolones are a class of antibiotic agents that act by inhibiting bacterial DNA gyrase. Different factors combine to raise teratogenic and fetotoxic concerns regarding their use during pregnancy. Mammalian DNA shares similar topoisomerases with micropathogens. Together with the fact that fluoroquinolones cross the human placenta (5), they can theoretically have mutagenic and carcinogenic effects on the developing fetus. Furthermore, the quinolones have a high affinity for cartilage. Studies with beagle dogs and guinea pigs have demonstrated arthropathy of weight-bearing joints after the administration of 200 and 1,000 mg of pipemidic acid and oxolonic acid, respectively (6). This observation was further supported by human case reports (2, 3). A recent study suggested a high malformation rate (11.9%) among children who had been exposed to ofloxacin in utero (11). Moreover, 5 reported cases of abdominal wall malformations are an alarming sign in light of the published background rate of these malformations: 2 to 5/10,000 population. Finally, higher rates of fetal distress and delivery by cesarean section were reported for a cohort of 38 women exposed to quinolones compared to the rates for controls exposed to nonteratogenic drugs (1).

In light of the increasing levels of resistance of many micropathogens to the antibiotics commonly prescribed during pregnancy, the clinical use of fluoroquinolones has been increasing substantially. Together with the fact that half of the pregnancies in North America are unplanned (12), the safety of fluoroquinolones during pregnancy is an increasing concern.

Presently, the available data regarding the use of quinolones during pregnancy are very limited: only the results of one prospective controlled study with a very limited sample size ($n = 38$) (1) and an uncontrolled survey (11) have been reported. Therefore, we initiated a multicenter, prospective controlled study to evaluate the potential teratogenic and fetotoxic concerns related to the use of fluoroquinolones during human pregnancy.

MATERIALS AND METHODS

We enrolled 200 women who called one of four teratogen information services to obtain information about the potential risks of drug use during pregnancy. These centers included Motherisk (Toronto, Ontario, Canada), Teratogen Information Service (Tampa, Fla.), Philadelphia Pregnancy Healthline (Philadelphia, Pa.), and Centro Regionale d'Informazione sul Farmaco (Milan, Italy). The data collection and follow-up methods were consistent among the centers, which used a structured questionnaire.

Data were collected at the time of exposure and before pregnancy outcome was known and included maternal age, gravity, parity, number of past sponta-

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neous and therapeutic abortions, smoking and alcohol consumption habits, drug exposure of interest (i.e., quinolone dose, timing, and indication for and duration of therapy), and maternal and genetic history.

All women and/or physicians were called after the expected date of delivery for a follow-up telephone interview that collected information regarding the outcome of the pregnancy, perinatal complications, birth weight, physical findings, any birth defect, and gross motor developmental milestone achievements according to the Denver Developmental Scale.

As a control group, we recruited 200 pregnant women who were counseled at Motherisk for the use of antibiotics that are known to be nonteratogenic and nonembryotoxic to account for the potential adverse effects of the infections themselves. Controls were matched for maternal age (±3 years), smoking and alcohol consumption habits, indication for and duration (±3 days) of therapy, and trimester of exposure. All women in the control group were followed up in a similar manner.

Our primary outcome of interest was the rate of major malformations, as defined by Marden et al. (9). Secondary outcomes of interest were live-birth rates, the numbers of spontaneous and therapeutic abortions, the numbers of fetal deaths, gestational age at delivery, birth weight, and the presence of fetal distress (defined as the presence of meconium and/or abnormal fetal heart rate monitoring during delivery or the need for neonatal intensive care). For the analysis of major malformations, fetal organogenesis was defined as the period between the 4th and 13th weeks of gestation (10).

Each of the participating centers received ethics approval locally.

Statistical analysis. Data for the two groups are presented as means ± standard deviations. Continuous data between groups were compared by the Student *t* test and the Mann-Whitney rank sum test, as appropriate. Categorical data were compared by χ^2 analysis. The rates of major malformations were analyzed by the Fisher extract test. Relative risk and the 95% confidence interval were also calculated. Multiple linear regression analysis was used to study the effects of the daily dose and duration of quinolone therapy, indication for therapy, trimester of exposure, and smoking and alcohol consumption habits on gestational age. Multiple logistic regression analysis was used to investigate the effects of these variables on live-birth rates.

TABLE 1. Characteristics of mothers exposed to fluoroquinolones compared to those of mothers exposed to nonteratogenic antibacterials

Characteristic	Quinolone group (n = 200)	Nonteratogenic antibiotic group (n = 200)	P value
Maternal age (yrs)	30.8 ± 5.2	30.6 ± 4.7	0.12[a]
Gravity (no.)	2.2 ± 1.3	2.1 ± 1.3	0.10[a]
Parity (no.)	0.9 ± 1.0	0.7 ± 0.9	0.83[a]
Spontaneous abortion (no.)	0.2 ± 0.5	0.3 ± 0.7	0.02[a]
Therapeutic abortion (no.)	0.1 ± 0.4	0.1 ± 0.4	0.55[a]
Nonsmoking status (%)	86.2	85.7	0.96[b]
No alcohol consumption (%)	99.2	94.7	0.07[b]
Concurrent drug therapy (%)			
Antiemetic or antipeptic agents	16.5	18.0	0.69[b]
Analgesics	10.0	12.0	0.52[b]
Antidepressants	1.0	1.5	0.97[b]
Folic acid supplementation	24	20	0.62[b]

[a] Mann-Whitney rank sum test.
[b] χ^2 test (with Yates correction).

RESULTS

Data for a total of 200 women exposed to fluoroquinolones during pregnancy were collected. Seventy-six (38%) of the women were from Toronto, 52 (26%) were from Philadelphia, 40 (20%) were from Tampa, and 32 (16%) were from Milan.

To exclude the possibility of selection bias, maternal characteristics were compared by using a cross-center analysis: maternal age, gravity, parity, the rate of previous spontaneous and therapeutic abortions, and smoking and alcohol consumption habits were not statistically different among the women at the participating centers.

One hundred five women (52.5%) were exposed to ciprofloxacin, 93 (46.5%) were exposed to norfloxacin, and 2 (1%) were exposed to ofloxacin. Information on treatment indication was given for 154 of the women: 69.4% of the women were treated for urinary tract infections, 24% were treated for respiratory tract infections, and the other 6.4% were treated for skin infections (n = 6), osteomyelitis (n = 2), breast abscess (n = 1), and a ruptured ovarian cyst (n = 1).

One hundred thirty-six women were exposed to quinolones during the period of organogenesis (4 to 13 weeks of gestation), 34 women were exposed during the second trimester (13 to 26 weeks of gestation), and 30 women were exposed during the third trimester (26 weeks to delivery). The treatment doses ranged from 400 to 800 mg for norfloxacin, 500 to 1,000 mg for ciprofloxacin, and 200 to 400 mg for ofloxacin.

There were no differences in characteristics among the women in the study and control groups (Table 1) except for a higher reported rate of previous miscarriages in the control group. Concurrent drug therapy did not differ between the study and the control groups: 16.5% of the women in the quinolone group used antiemetic or antipeptic agents (antihistamines, pyridoxine, H_2 blockers, antacids), whereas 18.0% of the women in the control group used such agents (P = 0.69). Analgesics (acetaminophen, nonsteroidal anti-inflammatory agents) were used by 10.0% of the women in the quinolone group, whereas they were used by 12.0% of the women in the control group (P = 0.52), and antidepressants were taken by 1% of the women in the quinolone group and 1.5% of the women in the control group (P = 0.97). In addition, four women in each group reported the use of salbutamol inhaler to control mild asthmatic attacks. One patient in the quinolone group used verapamil throughout pregnancy to control her essential hypertension, and one patient in the control group had used bromocriptine to treat her prolactin-secreting pituitary microadenoma.

There was a trend toward a higher rate of therapeutic abortions among the quinolone-exposed women (9 of 200 versus 2 of 200 for the control group; P = 0.06). This is reflected in a lower live-birth rate among the quinolone-exposed women (173 of 200 versus 188 of 200 for the control group; P = 0.02). However, of all the potential drug-related factors (i.e., daily dose, duration, trimester of exposure, and indication) analyzed by multiple logistic regression, none had a statistically significant predictive value on the live-birth rate. Gestational age at delivery was significantly lower among the quinolone-exposed women: 39.3 ± 2.0 weeks versus 39.8 ± 2.0 weeks among the women in the control group (P = 0.02). However, there were no differences in rates of prematurity. Similarly, there were no differences in pregnancy outcome with respect to the rates of spontaneous abortions, birth weight, and fetal distress (Table 2). Multiple regression analysis demonstrated no significant predictive effect of each of the potential risk factors on gestational age at delivery.

We found no differences in the rates of major malformations between children exposed to fluoroquinolones during organogenesis and children of mothers in the control group: 3 of 133 versus 5 of 188 (P = 0.54; relative risk = 0.85; 95% confidence interval, 0.21 to 3.49).

The major malformations noted in the quinolone group were two cases of ventricular septal defect and one case of patent ductus arteriosus. Among the controls, the major malformations included two cases of ventricular septal defect, one case of atrial septal defect with pulmonic valve stenosis, one

TABLE 2. Pregnancy outcome for women exposed to fluoroquinolones during pregnancy compared to that for controls exposed to nonteratogenic antibiotics

Outcome or characteristic	No. of women with the following outcome/ total no. of women:		Relative risk (95% confidence interval)	*P* value
	Quinolone group	Nonteratogenic antibiotic group		
Live births	173/200	188/200	0.92 (0.86–0.98)	0.02[a]
Spontanous abortion	18/200	10/200	1.80 (0.85–3.80)	0.17[a]
Therapeutic abortion	9/200	2/200	4.50 (0.98–20.57)	0.06[a]
Vaginal delivery	145/173	148/188	1.06 (0.96–1.18)	0.27[a]
Premature birth	11/173	13/188	0.92 (0.42–2.00)	0.99[a]
Birth weight, <2,500 g	7/173	9/188	0.85 (0.32–2.22)	0.93[a]
Fetal distress	22/173	27/188	0.89 (0.52–1.49)	0.76[a]
Delivery by cesarean section	28/173	40/188	0.83 (0.61–1.13)	0.21[a]
Gestational age	39.3 ± 2.0[b]	39.8 ± 2.0[b]		0.02[c]
Birth weight	3,452 ± 537[d]	3,477 ± 608[d]		0.92[c]

[a] χ^2 test (with Yates correction).
[b] Units are in weeks of gestation.
[c] Mann-Whitney rank sum test.
[d] Units are in grams.

case of hypospadias, and one case of displaced hip. The maternal reports of all major malformations were confirmed by their physicians in writing, and the confirmation included the specific diagnosis.

Gross motor developmental milestones achievement according to the Denver Developmental Scale did not differ between the two groups (Table 3).

DISCUSSION

The association between fluoroquinolones and arthropathy, although observed in immature animals and rarely reported in humans, has resulted in the restricted use of fluoroquinolones during pregnancy. Data from recent reports suggest that quinolone administration to children and adolescents with cystic fibrosis is safe on the basis of both clinical and magnetic resonance imaging assessments (4). However, since these observations have focused on children and adolescents, it is unclear whether in utero exposure to quinolones and their potential deposition in fetal cartilage are associated with any long-term musculoskeletal dysfunctions. Our data, which we obtained using the Denver Developmental Scale, suggest that in utero exposure to quinolones is not associated with clinically significant major musculoskeletal dysfunctions. This tool is very limited in evaluating subtle joint changes that would have been detected only by sensitive methods. Magnetic resonance imaging of weight-bearing joints of children exposed to quinolones in utero is in progress in our attempt to address this concern.

In designing this study, we aimed at controlling for the indication for the drug so that the putative effects of the infections would not be attributed to the quinolones. The prospective nature of this study aimed at obviating recall and selection bias.

The rate of major malformations in among children born alive and exposed to quinolones during the first trimester was within the expected normal range (1 to 5%) and was numerically identical to that among children in the control group. Importantly, we did not observe any major or minor abdominal wall malformations. The sample size of our study has a power to detect a 3.5-fold increased risk of major malformations, assuming a baseline risk of 3% with a power of 80% and an α value of 0.05. These data suggest that despite the limited strength of this study to detect a minimal increased risk above the baseline, it is very unlikely that fluoroquinolones are a major human teratogen.

The shorter length of gestation observed in the quinolone group is probably of no clinical significance because the other parameters such as birth weight and the rates of occurrence of birth weights below 2,500 g did not differ between the two groups. Moreover, multiple regression analysis indicated that quinolone therapy-related factors such as the daily dose, the duration of and indication for therapy, and the trimester of exposure probably do not explain the shorter length of gestation age in this group. The higher rate of therapeutic abortions observed in the quinolone-exposed women compared to that observed in their controls may be secondary to misinformation and misperception of a major risk related to their use during pregnancy. However, other medical and especially nonmedical reasons can also account for this finding. The possible high misperceived risk related to quinolone use during gestation probably stems from several statements found in the literature: the Compendium of Pharmaceuticals and Specialties (1a) states that "ciprofloxacin should not be used in pregnant women unless the likely benefits outweight the possible risk to the fetus." Another recent publication (11) claims that "quinolones should still be regarded as contraindicated during pregnancy," although these data were from an uncontrolled study. It is our experience that such information often leads to excess anxiety and unnecessary therapeutic abortions. It has been demonstrated that both pregnant women and their physicians tend to assign high teratogenic risk to a variety of compounds not known to cause harm in humans (7). Moreover, early intervention has been shown to prevent unnecessary pregnancy terminations by correcting misinformation, thus de-

TABLE 3. Acquisition of milestones defined by the Denver Developmental Scales

Milestone	Age (mo) at which milestone was acquired		*P* value[a]
	Quinolone group	Nonteratogenic antibiotic group	
Lifting	2.2 ± 1.0	2.3 ± 1.1	0.21
Sitting	5.9 ± 1.7	5.8 ± 1.2	0.24
Crawling	7.2 ± 1.6	7.2 ± 1.4	0.40
Standing	8.7 ± 1.8	8.7 ± 1.8	0.45
Walking	11.2 ± 1.7	12.0 ± 2.3	0.41

[a] Student *t* test.

creasing the high misperceived risk by women exposed to nonteratogens (8).

In the era of increasing resistance of many micropathogens to different antibacterial agents, quinolones should not be prescribed as first-line agents for the treatment of uncomplicated urinary tract infections and should definitely not be prescribed for upper respiratory tract infections. However, in cases of infections with resistant micropathogens or complicated urinary tract infections during pregnancy, when the use of quinolones is mandatory, or in cases of inadvertent fetal exposure to fluoroquinolones (unplanned pregnancies), our data indicate that their benefits outweigh the risks to the fetus and that therapeutic abortions due to fetal exposure to these agents is unjustified.

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