Use of Danish Health Registries to Study Drug-induced Birth Defects

– A Review with Special Reference to Methodological Issues and Maternal Use of Non-steroidal Anti-inflammatory Drugs and Loratadine

PREFACE

This thesis is based upon the work performed at the Department of Clinical Epidemiology, Aarhus University Hospital, Denmark.

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ABBREVIATIONS

DNRP	The Danish National Registry of Patients
DMBR	The Danish Medical Birth Registry
TIS	Teratology Information Service
NSAIDs	Non-steroidal anti-inflammatory drugs
SSRI	Selective serotonin re-uptake inhibitors
CI	Confidence interval
CNS	Central nervous system
OR	Odds ratio
POR	Prevalence odds ratio
RR	Relative risk

STRUCTURE OF THE THESIS

The present thesis consists of nine chapters and two appendices. Chapter 1 contains an introduction to studies of drug-induced birth defects. Towards the end of the chapter the aims are defined as 1) to provide an overview of methodological problems related to using health care databases for studying safety of drug use in pregnancy, 2) to study the safety of a commonly used drug in pregnancy, such as non-steroidal inflammatory drugs, and 3) to study the association between maternal use of a commonly used anti-allergic drug, loratadine, and the risk of hypospadias. Chapter 2 examines methodological issues in studies of drug-induced birth defects. Four studies examining the safety of drug-use during pregnancy are presented in chapter 3 (non-steroidal inflammatory drugs) and chapters 4, 5 and 6 (anti-allergic drugs). Chapter 7 covers the conclusions and the perspectives for future registry-based research within drug-induced birth defects. In chapter 8 the summary of the thesis is presented and chapter 9 covers a Danish summary of the thesis. In appendix I further methodological considerations and analyses in relation to the safety of non-steroidal inflammatory drugs are presented. Appendix II covers the publications originating from this thesis.

CHAPTER 1

Scope of the thesis

Teratogenesis is defined as the dysgenesis of fetal organs as evidenced either structurally or functionally (for example, brain function.[1,2]) Typical manifestations of teratogenesis are fetal restricted growth or death, carcinogenesis, and birth defects. Some birth defects might be minor, but major birth defects can be life-threatening, require surgery or have serious cosmetic and functional consequences.[1]

Birth defects, known throughout the human history, occur with a prevalence of 3-5% of live-born infants,[3] but little is known about the causes of birth defects. Through about the first half of the 20th century, placenta was believed to protect the fetus from exogenous agents. Then a number of findings dispelled this notion.

First, Gregg in 1941 reported that rubella infection in pregnancy caused a specific pattern of birth defects among the exposed children.[4] Further, the so-called thalidomide disaster showed potential teratogenicity of medicinal agents. Thalidomide was marketed at the end of the 1950s as a hypnotic drug and was claimed to be safe for use in pregnancy. Shortly after thalidomide's entering the market, a substantial increase was seen in the prevalence of a very rare birth defect called phocomelia, characterized mainly by reduction of extremities.[5] On 16 December 1961, McBride, in a letter to the Editor in the Lancet, described a case series of children born with major limb reduction and other defects.[6] All the malformed infants' mothers had used thalidomide during the pregnancy. Because the birth defect is so uncommon, the finding strongly suggested a causal link with thalidomide, but thousands of children over many years were born with this birth defect before the causal link was confirmed,[5] despite a high prevalence of phocomelia among the exposed infants.

The thalidomide disaster led to another extreme of common belief: that every drug was potentially a new thalidomide. However, during almost 50 years following the thalidomide disaster, only 30-40 drugs have proven to be teratogenic in humans[1,7] (table 1.1). Several drugs, including salicylate, glucocorticoids and anti-histamines,[8] have been thought to be teratogenic but large studies did not confirm the initial suspicion. A recent example of a medicinal agent being under suspicion for teratogenicity is the reported association between the anti-allergic drug loratadine and risk of hypospadias, which is one of the topics in this thesis.[9]

Table1.1 Selected commonly used drugs with proven teratogenic effect.

Teratogenic drug	**Birth defects**
Antithyroid drugs	Fetal and neonatal goiter and hypothyroidism, aplasia cutis (with methimazole)
Carbamazepine	Neural-tube defects
Hypoglycemic drugs	Neonatal hypoglycaemia
Isotretinoine	CNS, craniofacial, cardiovascular and other defects
Lithium	Ebstein's anomaly
Misoprostol	Moebius sequence
Non-steroidal anti-inflammatory drugs	Contraction of the ductus arteriosus, necrotizing enterocolitis
Phenytoin	Growth retardation, CNS deficits
Tetracycline	Teeth and bone defects
Trimethadione	Facial and CNS defects
Valproic acid	Neural-tube defects
Warfarin	Skeletal and CNS defects, Dandy-Walker syndrome

Since the thalidomide disaster, most doctors have been aware of the potential risk of giving drugs to women during the first trimester of pregnancy. Doctors are faced with a difficult clinical decision as they have neither general nor defensive guidelines due to insufficient or even absent knowledge about possible side effects.[10] On the one hand, insufficient treatment of the mother can have severe clinical consequences since untreated disease can present a risk for both the mother and the child.[1] On the other hand, the vulnerable fetus must be protected against potential fetotoxic drug effects. Furthermore, uninformed fears of fetal damage due to drug use may lead to unjustified pregnancy terminations.[11]

More than half of all pregnant women take medications, and if vitamins and other dietary supplements are included, almost all pregnant women will be considered medication users.[12-14] Therefore any association between drug use in pregnancy and increased risk of birth defects has major public health and clinical implications. Whether too many or too few are treated is unknown, but some pregnant women may not be treated optimally, including some who are treated with drugs they should not use.[7] A small proportion of medicines and supplements used during pregnancy probably have unknown adverse effects that outweigh

their therapeutic benefits. Since drugs are not tested in pregnant women before being released on the market, they are only gradually introduced for use in pregnancy. Their effects on reproductive outcomes are not reported or utilized in any systematic way in most countries.[7]

Drugs cross placental barrier, and because of rapid cell growth and extremely complicated cell differentiation, a fetus is more vulnerable to potential adverse drugs effects than a neonate or an adult.[10] Substances that are not very toxic for adults, such as thalidomide or high doses of retinol, may cause serious damage to the fetus.[7] When they enter the fetal micro-environment, chemicals may cause fetal death, birth defects, functional disorders, reduced growth, or change in the programming, which may influence susceptibility to diseases later in life.[15] It has been known since 1971 that prenatal drug exposure may be carcinogenic: diethylstilbestrol given during pregnancy has caused clear cell adenocarcinoma of the vagina in young women with a predisposition to the disease.[16-18]

After the thalidomide disaster, possible teratogenic effects of drugs began to receive close attention owing to their potentially serious consequences for the child, the family and the society. Information on side effects during pregnancy usually stems from animal studies, mostly those on rats and rabbits, but these studies focus primarily on fertility, spontaneous abortion and structural defects.[7] Furthermore, these data cannot be extrapolated uncritically onto human populations because species differ in metabolisms, biologic interactions, and susceptibility to drugs' teratogenicity and reproductive toxicity. Thalidomide is a classical example of limitations of certain animal studies with respect to the prediction of teratogenicity in humans.[10] With few exceptions, e.g., vitamin derivates, androgens, valproate and antibiotic drugs, all teratogenic effects have been discovered in human studies earlier than in animal studies.[1,10]

Most fetal organs are formed during 5-12 week of gestation, which is why they are particularly vulnerable to teratogenic exposure during this period.[7] At the same time, women are often unaware of the pregnancy in the first period of embryogenesis, making it difficult to prevent drug intake in that period. Later in pregnancy the fetus may be likewise exposed both to the toxic and pharmacologic effects of the drug. The brain and the nervous system continue to develop during the whole fetal period as well postnatally, thus being a lingering target for teratogenic effects of drugs.[10] Randomized trials of medicines are not conducted among pregnant women for ethical reasons.[19] Therefore observational studies need to supplement animal models in creating the optimal background for the clinical decision making regarding drug use in pregnancy.

Spontaneous notifications play an important role as indicators in the surveillance of side effects of drugs, but they cannot be regarded as sufficient and comprehensive because neither the frequency of notification nor the size of the population at risk is known.[7] Pharmacoepidemiology, combining epidemiological

methods and principles in clinical pharmacology research, is therefore a fast-growing discipline. Most pharmacoepidemiological studies consider specific birth defects, with dramatic effect on the sample size requirements both for estimating risks (reducing type I error rate) and providing assurance of the safety (reducing type II error rate).[3] Only a fraction of cohort members is expected to use a specific drug (if they are not specifically selected according to drug use), while most of the cohort members will not develop the disease under study.[7] Thus, cohort studies of rare outcomes, such as birth defects, need to be very large, as majority of the cohort members provide little information.[20]

The overall prevalence of birth defects is, as mentioned earlier 3-5%, depending upon definition and diagnostic routines, but prevalences of specific types of birth defects do not exceed 5-15 per 1,000 live births, even for birth defects considered common, such as congenital dislocation of the hip, ventricular septal defects, neural tube defects and cleft lip/palate or club foot.[7] Therefore, until recently birth defects have been studied using the case-control design. Since a prospective case-control study requires participants' informed consent, non-response and differential recall may produce selection and information bias.[21] The existing case-control monitoring systems have a participation rate of 70-90%, which is sufficiently low to cause serious bias estimates of effects of medication use; in many countries the participation rate may be even lower.[21] Even in large case-control studies the statistical precision is limited for infrequently used drugs. Only few studies are large enough to provide meaningful results for specific birth defects.

Since it is usually impossible for methodological, practical and economic reasons to collect ad hoc cohort data in sufficiently large populations, pharmacoepidemiological research has been largely relying on data from computerized health care databases in the United States, Great Britain and Canada.[22-24] However, those databases have only a limited utility for studying teratogenic effects of drugs, because of lack of birth data, including that on birth defects.

Nordic countries have established a number of health care databases covering decades of population-wide follow-up. The establishment, in Denmark, of the National Population Registry in 1924 and introduction of the Personal Registration Number (the CPR number used in the Central Personal Registry since 1968) allowed for personal identification of remarkable quality and for the possibility of collecting and linking information about the same person in independent databases.[25,26] This unique setup available in Nordic countries is not offered in systems of other countries. Over the last 40 years, Denmark has developed several administrative health care databases as part of the public administration of the health care system and related areas, used for management, claims, planning, surveillance, and – albeit less often – research.[27] The Danish National Board of Health has collected electronic information on prescriptions redeemed over the last 10-20 years.[28] We have linked those prescription databases to the Danish Medical

Birth Registry (DMBR), to the regional hospital registries, and to the Danish National Registry of Patients (DNRP) aiming to develop several cohorts for studying safety of drugs use in pregnancy.[29-38] Use of such existing routinely maintained databases in medical research offers many advantages, the main one being readily available collected data, implying that a study with a large number of subjects can be done in a fraction of time that would be required for an equivalent study with primary data collection.[39-41] Furthermore, the costs of such projects are low, particularly in comparison with prohibitively expensive primary data collection on comparable material. Other major advantages of the registries in relation to teratogenic research are:[39]

1. Large sample size allows for greater precision of risk estimates and enables the study of rare drug exposures and outcomes.
2. Completeness of many registries with respect to capturing the members of the target population largely prevents selection bias.
3. Independence of data collection of any research hypothesis leaves less room for certain types of bias, e.g. recall, non-response and bias due to effect of the diagnostic process of the intention caused by the research question.
4. Possibility of very long-term follow-up. A number of diseases will appear many years after the action of a causal exposure, and the existing registries are often suitable source (and sometimes the only available one) for studying of health conditions with a long induction and/or latent periods.

Registry-based data are not without limitations, which are often ignored.[39] They are related to data selection and quality, since the methods and the data collection are predetermined, not controlled by the researcher, and sometimes impossible to validate.

Therefore the aims of the present thesis are:

- To provide an overview of methodological problems related to using health care databases for studying safety of drug use in pregnancy (chapter 2).
- To study the safety of drugs commonly used in pregnancy, such as non-steroid inflammatory drugs (chapter 3).
- To study the association between maternal use of a widely prescribed anti-allergic drug, loratadine, and the risk of hypospadias (chapters 4, 5 & 6).

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CHAPTER 2

Use of health care databases to study association between maternal medication in pregnancy and risk of birth defects: Methodological issues

This chapter has not been published as a paper.

Introduction

More than half of all pregnant women take medications at some point during their pregnancy,[1-3] while nearly all drugs and their metabolites cross placental barrier.[4] For the fetus, medication's metabolites may be more toxic than the medication itself, as was seen in the case of thalidomide (for current bibliography see http://www.nlm.nih.gov/archive/20040831/pubs/cbm/thalidomide.html#300). The fetal exposure level is determined by the agent's absorption, metabolism, distribution and elimination in the maternal and in the fetal organisms.[4,5] In the woman, physiologic changes of pregnancy alter typical drug metabolism: on the one hand the overall concentration of the drug in maternal circulation is lower because of the pregnancy-induced increase in the blood volume; on the other hand, the increased blood volume and decreased concentration of albumin slow down the drug metabolism and elimination.[4,5]

As birth defects are rare, case-control design has been commonly used for studying determinants of birth defects. In addition to the well known shortcomings of the case-control approach[6] (differential recall of self-reported medication use; selection bias due to non-participation), case-control studies enable estimation of relative effect measures (rate ratios, risk ratios), and do not enable measurement of absolute risks. Clinically and from the public-health standpoint, it is important to have information on risks of birth defects according to groups defined by cohorts of pregnant medication users.

Large computerized databases covering entire populations are becoming increasingly available. Thanks to large numbers of observations, studies can be done using the cohort design, and can be accomplished relatively quickly and inexpensively.[7] Examples of data sources potentially suitable for studying teratogenic effects of medications include claims databases; electronic medical records; population registries; and teratology information services. After brief description of these data sources, we focus on common epidemiologic biases – selection bias, information bias, and confounding[8] – as applied to studies that use electronic sources to study teratogenicity of drugs.

Computerized databases enabling study of teratogenic effects of drugs

Claims databases and electronic medical records

Claims databases track a person's use of the health care system for reimbursement purposes. In the US, claims data from Medicaid – government-sponsored health care program for low-income individuals – have been used for pharmacoepidemiologic studies since the early 1980s. Fetal outcomes after in-utero exposure to benzodiazepines[9] and ACE inhibitors[10] have been studied using the Medicaid database. While data on medication use in claims databases have high quality,[11] the validity of the data on offspring outcome is worse; in particular, outpatient diagnoses appear to be the least reliable.[12]

Medical records increasingly become electronic. Perhaps the best-known example of a computerized medical-record database is the General Practice Research database (GPRD, http://www.gprd.com). GPRD has collected information on more than 4 million patients in Great Britain and has data on referrals as well as findings and diagnoses made during hospitalizations and outpatient visits at general practitioner (GPs). Prescriptions generated by the GPs are also part of the patient's electronic record, enabling the study of potential teratogenic effects of medications[13] (for example, the study of birth defects in offspring of epileptic women treated with anticonvulsants[14]).

Swedish and Norwegian prescription and birth registries

Medical registries in the Nordic countries provide opportunities of studying effects of medicinal agents in pregnancy in large unselected cohorts. The Swedish Medical Birth Registry has collected data on antenatal care, delivery and the neonatal outcome covering nearly all births in Sweden since 1 October 1994.[15] Medication use in this database is measured by the pregnant woman's self-report to a midwife during her first antenatal-care visit (usually week 10-12). Using this data source, Asker et al. examined the relation between the use of antiemetic drugs during pregnancy and birth outcome.[15] However, self-reported nature of drug use data is a major drawback of these data, since drug use may be under-reported by pregnant women. The Norwegian Prescription Database,[16] founded in 2004, is linkable with The Medical Birth Registry of Norway,[17] enabling population-based studies of drug teratogenicity without relying on self-report.

Danish registries

In Denmark, prescription medications have been registered, since 1 January 1995, in a nationwide electronic prescription database, maintained by The Danish Medicines Agency. The database records prescriptions for all reimbursed drugs dispensed at all pharmacies in Denmark. In the Danish county of North Jutland similar data have been collected since 1 January1989 and they have been stored in a prescription research database maintained by the Department of Clinical Epidemiology, Aarhus University Hospital. In addition, research prescription databases from other counties have been stored in the department: for Aarhus county, since 1 January 1996 and for Ringkjøbing and Viborg counties, since 1 January 1998. The four county databases cover approximately 30% (~1.6M) of the Danish population and enable long-term follow up spanning in some cases more than one generation.

The Danish Medical Birth Registry (DMBR) tracks all live and still births in Denmark since 1 January 1973 and stores data collected by midwives and doctors attending deliveries.[18] Birth defects can be ascertained both from the DMBR and from the DNRP.[19] However, the registration of birth defects is incomplete in the DMBR, whereas the Danish National Registry of Patients (DNRP) is considered to have acceptable completeness and validity for research and monitoring of birth defects.[20]

All Danish databases are linkable on the individual level via the unique civil registration number (the CPR number[21]), assigned to at birth.[22] Because the Birth Registry record of a newborn contains maternal CPR number as one of the variables, it is possible to assemble cohorts of medication users among women giving birth and to prospectively measure outcomes among the offspring recorded in the DNRP.

Teratology information service

Another way of compiling data on pregnant women into registries is on the basis of a teratology information service (TIS). Women typically contact a TIS in early pregnancy or while planning a pregnancy to obtain information on the safety of drugs. The TIS then records information on demographic, obstetric, medical, and drug-exposure history.[23] In the first year following the expected delivery date, the TIS conducts a follow-up interview. Moretti et al. conducted a multi-center study of effect of maternal loratadine exposure on the risk of major birth defects, enrolling patients from TIS in Canada, Israel, Brazil, and Italy.[23] However, just as traditional epidemiologic studies, studies based on TIS may suffer from self-referral bias and losses to follow-up.

Sources of Bias

Large numbers of observations available from population databases reduce random error around estimates of effect obtained in studies that use these data. Precise estimates can be invalid due to systematic errors introduced while collecting, measuring, or analyzing data. Thus, while random error can be remedied by increasing sample size, systematic error cannot.[24] Systematic error (bias) can lead to over- or underestimation of the true association between the exposure (to medication while in-utero) and the outcome (birth defect). Three types of bias may affect epidemiologic studies: selection bias, information bias, and confounding bias. We describe each type of bias as applied to study of potential teratogenic effects of medicinal agents using large electronic databases.

Selection Bias

In an ideal cohort study investigator aiming to examine potential teratogenic effects of a medicinal agent would recruit cohorts of agent-exposed and agent-unexposed women at or before conception and count malformation events among the fetuses throughout gestation, at birth, and several years postnatally. Incidence rate of a birth defect in the ideal cohort study is the number of all fetuses or neonates with birth defects detected at any time during follow-up divided by the total person-time contributed by conceptuses. Censoring events would include induced abortion, extra-uterine pregnancy, miscarriage, or stillbirth.

In reality, neither reproductive outcomes nor overall person-time of the initial conception cohort are fully observable (respectively, the numerator and the denominator of the incidence rate). Often it is only possible to detect cases of birth defects from birth and onwards, and in some cases, at prenatal diagnosis, which is why the measure of occurrence in this setting has traditionally been prevalence, calculated as the proportion of malformed fetuses detected at each observed reproductive outcome, among all births (live and still).[25]

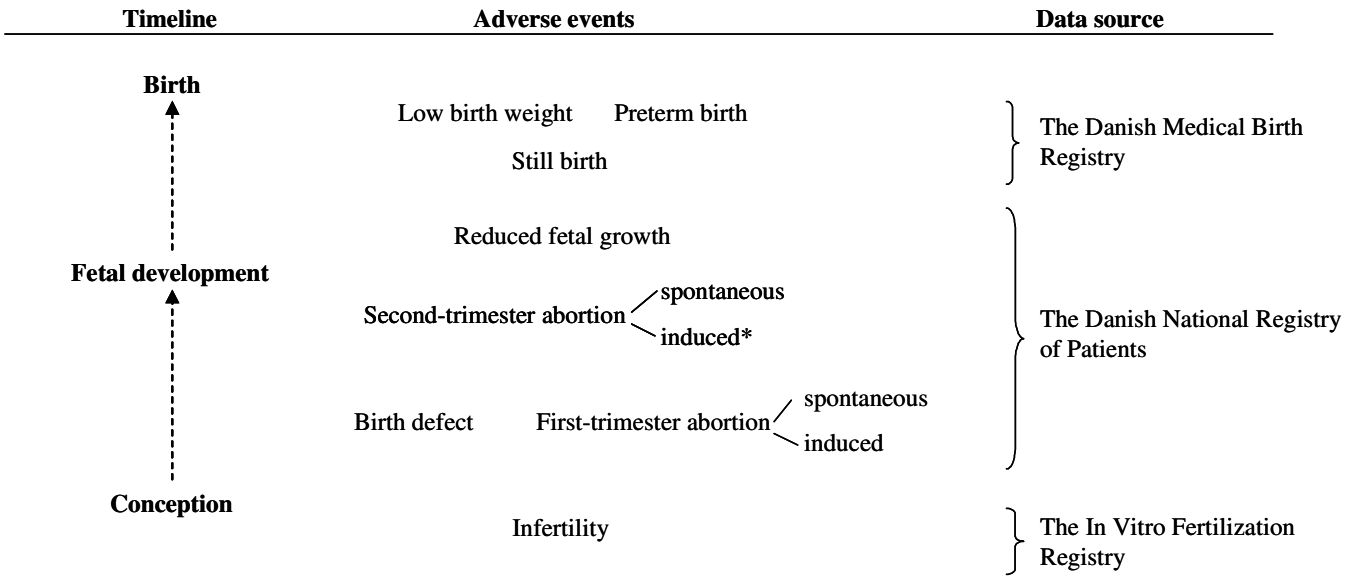

Figure 2.1 Time line for adverse events recorded in Danish registries from conception to birth. *Pregnancy terminated in week 12 following prenatal diagnosis or later due to for instance serious maternal complications.

In studying teratogenicity of medications, there are two major sources of selection bias[26]: spontaneous fetal loss (extra-uterine pregnancy, spontaneous abortion, stillbirth) and induced abortion (figure 2.1). Early in pregnancy (up to 15 days post-conception), spontaneous embryo loss may go unnoticed by the pregnant woman, but it could be caused by a fatal malformation.[27] (For example, while embryos with trisomy 21 – Down's syndrome – survive to birth, nearly all other recognized autosomal trisomies are incompatible with life, and affected fetuses are spontaneously aborted[28]). An unobserved malformation leading to early spontaneous fetal loss could potentially be caused by a teratogenic drug. To an investigator measuring prevalence of birth defects at birth the drug will not appear teratogenic because of the high early prenatal fatality rate.[29] Conversely, a medication exposure may enhance survival of fetuses with particular malformation without affecting the incidence of that malformation. At birth, the malformation would be more prevalent among offspring of users than among offspring of non-users of that medication, creating spurious appearance of teratogenicity.[29]

First-trimester elective pregnancy terminations (roughly 20% of conceptuses[30]) are largely unrelated to use of medication or suspected birth defects,[31] and are therefore unlikely to introduce selection bias. A

therapeutic second-trimester induced abortion may occur after a malformation detected by prenatal diagnosis. Availability and use of prenatal diagnosis varies geographically, determining the proportion of prenatally diagnosed cases of birth defects (e.g., 25% in Croatia vs. 88% in Paris[32]). Once detected, birth defects are terminated at rates that vary depending on local laws, severity of birth defect, and the long-term prognosis.[32] Up to 94% of fetuses with prenatally diagnosed fatal malformation (e.g., anencephaly) are terminated, as compared with 30% to 40% of fetuses with birth defects amenable to treatment (e.g., diaphragmatic hernia or transposition of great arteries[32]). Birth defects detected at prenatal diagnosis after week 12 have been recorded in the DNRP since 2006. Data from 2007 are shown in figure 2.2 and compared with the recorded number of birth defects among live birth detected within the first year of life.

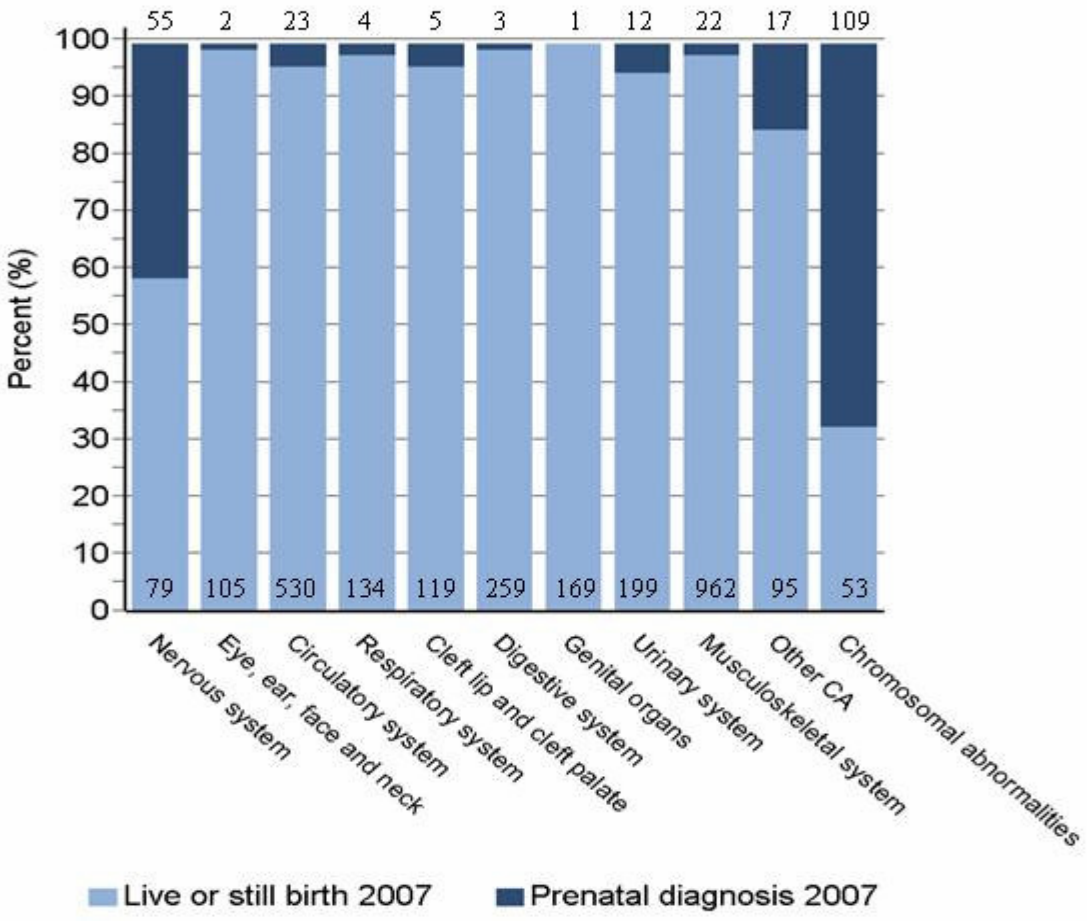

Figure 2.2 Data from the Danish National Registry of Patients and the Danish Medical Birth Registry in 2007. Birth defects detected and terminated following prenatal diagnosis after week 12, compared with birth defects recorded among live or still births after week 28 and within the first year of life. In total n=2,957 birth defects (absolute numbers are presented in brackets).

In order to reduce selection bias, it is important to include data on birth defects observed not only at birth (live or still) but, if possible, at abortion and during prenatal diagnosis.[28] In Denmark, it is possible to identify legal induced abortions between 1973 and 1994 from the National Registry for Induced Abortions.[33] Since 1977, hospitalized women undergoing spontaneous and induced abortions are recorded

in the DNRP. Figure 2.3 is based on data from 2007 and illustrates the distribution of abortions in the DNRP and live and still births from the DMBR by gestational week. Person-time contributed by these pregnancies can be included in calculations of incidence rates of birth defects.

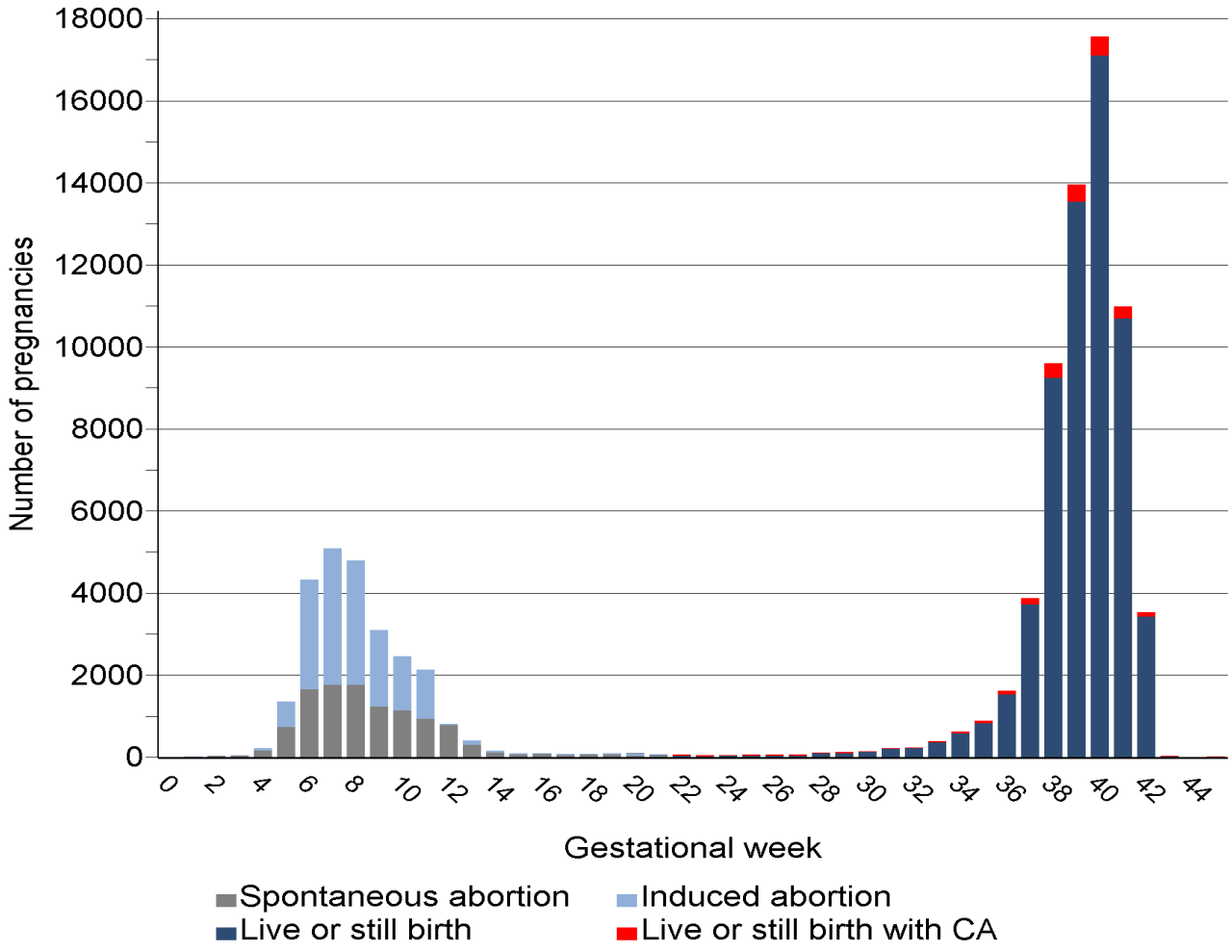

Figure 2.3 Data from the Danish National Registry of Patients and the Danish Medical Birth Registry in 2007. Distribution of spontaneous abortions, induced abortions and live or still births including birth defects by gestational week. In total 89, 639 pregnancies (28.4% ending in abortion).

The European network of population-based registries for the epidemiologic surveillance of congenital anomalies, EUROCAT,[25] has published a special report on prenatal diagnosis policies and procedures in different European countries.[25] Both prenatal diagnosis itself and associated pregnancy termination are becoming more widespread. According to a study in the United States, use of ultrasonography or amniocentesis for prenatal diagnosis has increased from 7% in the mid-1970s to almost 90% in the late-1990s. The study also found an increase in the rate of elective abortions for any malformation from 0.8% to 18%, with greater absolute increase seen among terminations for non-fatal birth defects (i.e., those likely to be observed at birth).[34] Women's demographic characteristics could influence access to and utilization of prenatal diagnosis.[34] Thus, the degree and direction of potential selection bias due to

prenatal diagnosis can be expected to vary according to demographic and health indicators, calendar time, and the type of malformation.

Information bias

Errors in measurement and/or recording of medication use, birth defects, or related variables cause misclassification of fetuses with respect to their in-utero drug exposure, presence of birth defects, or characteristics that may confound putative associations. Mechanisms of misclassification common to data recorded in electronic databases are discussed below.

Misclassification of medication use

Because prescription databases record dispensed medications for the purpose of reimbursement, their data quality is considered to be the 'gold standard' in relation to patient's self-report or physician's notes.[35] However, once dispensed, no information on adherence is available from a prescription database. Misclassification stems from erroneous assumptions regarding the fact, the timing, and the dosage of medication intake by pregnant women. A pregnant woman may decide not to take a dispensed medication at all, take it at a later date, or at a dosage that is different from prescribed. Furthermore, medications dispensed to pregnant women during hospitalizations are not, as a rule, recorded by outpatient pharmacies, leading to misclassification of fetuses as unexposed. Misclassification of timing of drug intake is an important limitation, given the short duration of gestation in general and even shorter duration of developmental time windows during which particular birth defects can plausibly occur as a result of medication exposure.

A particular bias stemming from misclassification of person-time spent in exposed and unexposed states is the so called 'immortal time bias'. Immortal time is 'a span of cohort follow-up during which, because of exposure definition, the outcome under study could not occur'.[36] An example of immortal time in the setting of intrauterine exposure to medication is classifying a fetus as exposed or unexposed in a dichotomous fashion based on whether or not the mother filled a relevant prescription. In order to become included in the medication-exposed cohort, the fetus had to survive until the date of prescription without birth defect of interest being detected; and therefore the time between conception and the date of prescription for the exposed fetus is "immortal". Treating the immortal time as exposed or excluding it from the analyses may produce biased estimates indicating apparently protective effect of medication with respect to the risk of the birth defect.[36]

Misclassification of birth defects

In contrast to electronic pharmacy data, electronic clinical and diagnostic data are generally considered inferior in quality to the corresponding medical records for the purposes of ascertaining events. The

proportion of true cases of birth defects captured by electronic sources (completeness, analogous to sensitivity[37]) may vary widely with the type of anomaly and type of data source.[20,38] Imperfect sensitivity alone does not necessarily cause bias: if data source used to ascertain birth defects contain no false-positive records of birth defects (100% specificity), relative estimates of effect will be unbiased, provided no other bias is at work.[8] Specificity of electronic records of birth defects is expected to be high.[39]

Misclassification of confounders

Errors in data regarding antecedents of both drug exposure and birth defect in question (confounding factors) hinder control of confounding by these characteristics, and consequently, produce effect estimates that are biased in the direction of the uncontrolled confounding (see discussion below on residual confounding).

Joint misclassification

Misclassification of medication use (exposure) or birth defects (outcome) is said to be non-differential if the proportion of fetuses with one misclassified variable is independent from their status with respect to the other variable.[8] Non-differential misclassification of exposure is expected to cause under-estimation of the relative effect (risk or rate ratio), if one exists (although an over-estimation due to chance cannot be ruled out[24]). For polytomous exposures, misclassification patterns are more complex.[40] Differential misclassification may produce bias either toward or away from the null.[8]

In reality, misclassification errors affect all study variables to some degree; therefore the direction and the magnitude of bias produced by joint misclassification are difficult to estimate. Methods and software are available to investigate and quantify the extent and direction of potential bias from misclassification of study variables based on different assumption regarding the nature of misclassification.[41-44] Sensitivity and specificity of electronic records with respect to accuracy of measuring study variables can be derived from validation studies; if not available, they can be investigator's guesstimates based available knowledge. The available methods tend to apply to simple situations, with dichotomous exposure, outcome and confounder variables; however, even rough quantification of biases is a step forward compared with common and often unwarranted assumption of misclassification producing bias towards the null.[41]

Confounding

Pregnant women use medication in a non-random fashion, whereby pregnant users and non-users of medications are likely to differ with respect to underlying disease and demographic characteristics. If these are also independent risk factors for a given birth defect they can confound the estimate of

association between the medication and the birth defect under study. Examples of potential confounding factors include geography, maternal age, race, socioeconomic status, co-medication and disease for which the medication is prescribed (see below, confounding by indication).

Unmeasured confounding

Factors that have not been measured or that are unknown to the investigator cannot be controlled in the analysis except indirectly if they are associated with a factor that was measured and can be controlled (in contrast to a randomized study, whereby successful randomization balances out known and unknown confounders). The usual methods to control confounding (standardization, matching, stratification, restriction, regression modeling) do not remove confounding by unmeasured factors. One way to deal with unmeasured confounding is by external adjustment[45] whereby effect of potential confounding on the observed effect estimate is estimated under an 'array of informed assumptions'[45] about the association between confounder, exposure, and outcome. Alternatively, one may obtain reliable estimate of a confounder summary score or a propensity score in a sub-study with more detailed covariate information and then use this "gold standard" score to correct the effect of the drug on outcome (in this case, birth defects) in the main study.[46]

Residual confounding

Residual confounding occurs when control of a set of variables used to measure confounders does not completely remove confounding by these measured characteristics. Residual confounding arises when a confounding factor is misclassified or when the corresponding variable is inadequately categorized.[47] The direction of bias due to residual confounding depends on the direction of confounding. If, after adjusting for a (misclassified) confounding factor, estimate of effect is closer to null than the crude estimate, one should suspect that controlling for a perfectly measured confounder would further reduce observed association, and may even nullify it. Alternatively, if controlling for part of the confounding effect only results in minimal changes in the estimate then residual confounding is unlikely to explain major part of an association. Theory and software have been developed to assess potential impact of imperfect confounding control on study results under different assumptions about the degree of confounder misclassification.[45,48]

Confounding by indication

Maternal disease may increase fetal risks regardless of medication use. It is therefore critically important to separate the effect of a given drug from the effect of the disease it treats (the indication). For instance, pre-gestational insulin-dependent diabetes has been associated with a strong teratogenic effect,[49] whereas

any improvement in metabolic control during pregnancy seems to reduce the risk of adverse fetal outcomes.[50] In order to rule out or avoid confounding by indication, one may examine risks of birth defects among offspring of mothers taking medications prescribed for different indications or in women with similar indications taking different drugs. These methods may only partially remove confounding by indication since use of different medications for the same indication may vary according to severity or etiology of disease, both of which may influence fetal risks.

One may deal with confounding by indication by taking advantages of the time-sensitive nature of the relation between medication and the feasibility of birth defect. The timing of critical embryonic and fetal events is very specific, with most birth defects occurring during a short time period within the first trimester. Thus, if some women are exposed to a drug only during second or third trimester and there is an increased prevalence of cardiac birth defects among their offspring, the causal relation between the medication and the malformation is biologically implausible since the exposure did not act until after the malformation has occurred (see, for example, a study of prenatal exposure to selective serotonin re-uptake inhibitors (SSRIs) as a risk factor of birth defects[51]). In addition, if cases of birth defects are considered as their own control in a case-crossover design, confounding by indication may in some situations be eliminated.[52] In this design drug use is measured and compared during two different time windows, usually during gestation. However, if drug use is not expected to be stable during the study period, which can violate the design-assumption, the case-time-control design can be used. This design is a modification of the case-crossover design and uses a control group to separate the time trend effect from that of drug use.[53] The case-crossover principles are considered to be a very promising new development in studies of drug-induced birth defects.[52]

Conclusion

In the absence of evidence, associations between particular variables are often assumed absent. Study of drug safety during pregnancy is an example of a public-health field where any type of effect – harmful, neutral, or protective – has important implications for pregnant women and their offspring. In discussing potential biases of 'positive' studies, for example, authors may assert that their results are likely underestimate, rather than overestimate, the true association (e.g., by nondifferential misclassification of exposure), implying that the true positive association is greater than they report. Since absence of an association between medicinal agent and birth defects is just as important as their presence, results biased in either direction may have negative public-health consequences. A downward bias, masking a true association between a medicinal agent and a birth defect would result in continued use of the harmful agent. By contrast, an upward bias that creates a spurious observed association between a truly safe medication and a birth defect may lead to limited treatment options available to pregnant women,

possibly affecting treatments for chronic conditions that in the absence of treatment may themselves detrimentally affect pregnancy outcome.

If the potential methodological problems are understood and effectively dealt with, it is possible to conduct quality studies of teratogenicity of medications using computerized health care databases. These data sources allow for cohort design, enabling estimation of prevalences and even incidences of birth defects in cohorts of pregnant users of medicinal agents.

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CHAPTER 3

Risk of adverse birth outcome and miscarriage in pregnant users of non-steroidal anti-inflammatory drugs: Population based observational study and case-control study

This chapter has been published as a paper: Gunnar Lauge Nielsen, Henrik Toft Sørensen, Helle Larsen, Lars Pedersen. Risk of adverse birth outcome and miscarriage in pregnant users of non-steroidal anti-inflammatory drugs: Population based observational study and case-control study. British Medical Journal 2001; 322: 266-270

INTRODUCTION

Anti-inflammatory drugs are among the commonest drugs prescribed to pregnant women.[1,2] All non-steroidal anti-inflammatory drugs are inhibitors of cyclo-oxygenase and can have adverse effects in both mother and fetus.[3] Some investigators have linked fetal exposure to aspirin or indomethacin with a higher risk of birth defects and low birth weight,[4,5] though other investigators have failed to confirm this.[6–9] The risk of adverse birth outcome in users of non-steroidal anti-inflammatory drugs other than aspirin and indomethacin has been examined only in studies with low numbers of participants, and few have been population based.[10]

As non-steroidal anti-inflammatory drugs are widely used, even a small increase in the risk of adverse effects may have major implications for public health. We examined the risk of adverse birth outcome among Danish women who had taken up prescriptions for non-steroidal anti-inflammatory drugs during pregnancy.

SUBJECTS AND METHODS

Study population

The study was conducted in the Danish county of North Jutland (population approximately 490,000). It included data on all women who between 1991 and 1998 had a live birth or a stillbirth after the 28th week of gestation or who had a miscarriage (including missed abortions). The data were obtained from the Danish birth registry and the county's hospital discharge registry. Risk of adverse birth outcome (birth defects, low birth weight, and preterm birth) was examined in a cohort study and risk of miscarriage in a case-control study.

Use of non-steroidal anti-inflammatory drugs

As part of its tax funded health care for all inhabitants the Danish national health service reimburses 50% of all expenditure on a wide range of prescribed medicines, including non-steroidal anti-inflammatory drugs (international anatomical therapeutical classification code M01A) prescribed at doses equivalent to 400 mg or 600 mg ibuprofen (doses equivalent to 200 mg ibuprofen may be purchased without a prescription). North Jutland is served by 33 pharmacies equipped with electronic accounting systems that are used primarily to secure reimbursement from the national health service. These systems include information on the anatomical therapeutical classification code, the amount of the drug prescribed, the personal identification number of the patient, and the date of dispensing the drug.[11] All data are transferred to the pharmaco-epidemiological prescription database of North Jutland, which holds key data on all reimbursed prescribed drugs sold at pharmacies in the county since 1 January 1991.[12] During the period studied indomethacin was regarded as the drug of choice to delay premature delivery. As this may introduce a confounding factor, our analyses both included and excluded data on women who took indomethacin during pregnancy. We validated data on the use of non-steroidal anti-inflammatory drugs

by verifying prescriptions in general practitioners' and hospital records of a randomly selected subset of 46 pregnant women.

Outcome data

Registries. The Danish birth registry, which comprises data collected by midwives and doctors attending deliveries, contains information on all births in Denmark since 1 January 1973.[13] The main data are maternal age, self reported smoking status, order of birth, gestational age, length and weight of neonate at birth, and personal identifiers for both mother and child.

We identified all cases of birth defects and miscarriage from the regional hospital discharge registry (established in 1977), from which data are transferred to the national Danish hospital discharge registry. The national registry comprises data on 99.4% of all discharges from Danish hospitals and includes 10 digit personal identifiers, dates of admission and discharge, the surgical procedures performed, and up to 20 diagnoses,[14] classified according to the Danish versions of ICD-8 (international classification of diseases, 8th revision) until the end of 1993 and ICD-10 after this date. The codes for miscarriage were 634.61, 643.8-9, and 645.1 in ICD-8 and O02 and O03 in ICD-10, and those for birth defects were 740.00-752.09, 752.29-755.59, and 755.79-759.99 in ICD-8 and Q00.0-Q52.9, Q54.0-Q64.9, and Q66.0-Q99.9 in ICD-10. Diagnoses of congenital dislocation of the hip and undescended testis were excluded because of their low validity.

The personal identifiers were used to link prescription records with both registries. Follow up, using the regional hospital discharge registry, ended on 31 December 1998.

Cohort analysis. The association between use of non-steroidal anti-inflammatory drugs and adverse birth outcome was studied in a cohort of women who had a live birth or a stillbirth after the 28th week of gestation. The women were divided into two groups according to the stage of gestation (based on information from the birth registry) at which they took up prescriptions for non-steroidal anti-inflammatory drugs: the “early pregnancy” group comprised women who took up prescriptions from 30 days before conception to the end of the first trimester and the “later pregnancy” group comprised women who took up prescriptions in the second or third trimesters. The reference group was all pregnant women who were not prescribed any kind of reimbursed medicine in the study period. To determine whether there was a dose-response relation, we compared the outcomes of pregnancies of women during which only one prescription of a non-steroidal anti-inflammatory drug was recorded with those of women in which more than one prescription was recorded.

Case-control analysis. We used a case-control study to determine any association between non-steroidal anti-inflammatory drugs and first recorded miscarriage. Cases were defined as first recorded miscarriages in women who had taken up a prescription for non-steroidal anti-inflammatory drugs in the 12 weeks before the date of discharge from hospital after the miscarriage. The control group was primiparous women who had live births. The first trimester was used as the exposure period in the control group. The

risk estimates were calculated for time intervals of 1, 2-3, 4-6, 7-9, and 10-12 weeks before the day of discharge after miscarriage. All non-steroidal anti-inflammatory drug prescriptions were categorized according to these periods.

Statistical analysis

Cohort study. We performed logistic regression analyses to estimate the risk of birth defects low birth weight (<2500 g), and preterm birth (<37 weeks) associated with non-steroidal anti-inflammatory drugs, adjusted for maternal age, birth order, and smoking status. We used data from the early pregnancy group to estimate the risk of birth defects and data from the later pregnancy group to estimate the risk of preterm birth and low birth weight (analysis of risk of low birth weight was restricted to full term births).

Case-control study. We performed logistic regression analyses to estimate the risk of miscarriage associated with non-steroidal anti-inflammatory drugs. We included as a variable the period of time from when the prescription was taken up to the day of discharge after the miscarriage, adjusting for maternal age.

RESULTS

Cohort study

A total of 1,462 women who had a live birth or stillbirth after the 28th week took up 1,742 prescriptions for non-steroidal anti-inflammatory drugs; 1,106 women took up prescriptions in early pregnancy and 997 in later pregnancy (table 3.1). Apart from a lower proportion of smokers among the women who were not prescribed any drugs, no other significant differences in the study variables were found.

We identified 46 birth defects in 1,106 pregnancies of women who took up prescriptions of non-steroidal anti-inflammatory drugs during early pregnancy (4.2% (95% confidence interval 3.0% to 5.3%)), compared with 564 in 17 259 pregnancies in the reference cohort (3.3% (3.0% to 3.5%)). Details of these birth defects are shown in table 3.4. The adjusted odds ratios of birth defects, low birth weight, and preterm birth among women who took up prescriptions of non-steroidal anti-inflammatory drugs were 1.27 (0.93 to 1.75), 0.79 (0.45 to 1.38), and 1.05 (0.80 to 1.39), respectively (table 3.2). There were no stillbirths among the women who took up prescriptions.

Comparison of pregnancies during which more than one non-steroidal anti-inflammatory drug prescription was taken up with those in which only one was taken up gave adjusted odds ratios for taking up more than one prescription of 0.66 (0.20 to 2.17) for birth defects, 3.09 (0.91 to 10.52) for low birth weight, and 0.65 (0.26 to 1.68) for preterm birth.

Fifty women had taken up prescriptions for indomethacin. Review of hospital records confirmed that the risk of miscarriage was an indication for the prescribing of indomethacin in 38 cases; in 10 use of indomethacin could not be confirmed, and one record could not be traced. Exclusion of these data did not change the risk estimates shown in table 3.2 (data not shown).

Case-control study

Table 3.3 shows the odds ratios for miscarriage, compared with pregnancies ending in a birth, in women who took up prescriptions for non-steroidal anti-inflammatory drugs. The ratio decreases as the time from taking up the prescriptions to discharge from hospital increases. Neither restricting the calculations to missed abortions only (ICD-8, 634.61 and 645.1; ICD-10, O02.1) nor inclusion or exclusion of pregnancies during which indomethacin was taken changed the risk estimates given in table 3.3 (data not shown).

Validation of non-steroidal anti-inflammatory drug use

To validate use of the drugs, we studied a randomly selected subgroup of general practitioners' records and hospital records for 46 pregnancies in the cohort study. In 71% of these pregnancies, the records indicated that non-steroidal anti-inflammatory drugs were prescribed, mostly for benign conditions of the muscles and skeleton.

DISCUSSION

We found no significant association between take up of prescriptions for non-steroidal anti-inflammatory drugs during pregnancy and risk of birth defects, low birth weight, or preterm birth. There was, however, a significant association with miscarriage.

The full and independent registration of prescriptions and birth outcome prevented selection bias and some types of information bias. In the cohort study potential misclassification in the registration of birth defects would be unlikely to be related to the prescribing of non-steroidal anti-inflammatory drugs. The case-control study was based on routinely recorded data and was independent of diagnosis, thus there was no risk of recall bias, which can invalidate case-control studies that rely on interviews.[15] Previous studies have shown high validity of data in both the prescription database and the birth registry.[16,17] In a recent, as yet unpublished study that was based on a review of hospital records in the period 1 January 1991 to 31 December 1995, we found that more than 80% of patients coded as having a birth defects in the regional hospital discharge registry were correctly coded. Data on the major confounding factors of maternal age, smoking status, and birth order were available in the cohort study; the case-control study, however, lacked data on smoking status.

We had no specific information on compliance. That the prescriptions for non-steroidal anti-inflammatory drugs were taken up at the pharmacy and paid for in part by the patient may improve compliance. Furthermore, a relevant indication for the use of non-steroidal anti-inflammatory drugs was documented in general practitioners' records in a high proportion of pregnancies. These drugs, however, are often used as short term analgesics and may be purchased over the counter, which may increase the likelihood of misclassification of women with respect to drug use and bias the risk estimates towards one.

Teratogens do not uniformly increase the risk of all birth defects, but rather of specific birth defects.[15] We did not find any specific trend in the distribution of birth defects, and we did not find evidence for a dose-response relation between mothers' use of non-steroidal anti-inflammatory drugs and adverse birth outcome. Like other researchers we did not find an increased risk of reduced fetal growth.[8,9]

Use of non-steroidal anti-inflammatory drugs in pregnancy is clearly associated with increased risk of miscarriage. We had no information about the gestational age at time of miscarriage. A critical factor in the case-control study, therefore, is the time period that was selected for the controls, as general practitioners may change their prescribing practice when they know that a woman is pregnant. Such a bias would probably be independent of any particular drug among drugs that have the same estimated risk profile; we therefore repeated the analyses for penicillin V instead of non-steroidal anti-inflammatory drugs and found an odds ratio of 1. This result, as well as the decreasing odds ratio with increasing time interval between time of prescribing of non-steroidal anti-inflammatory drugs and miscarriage, indicates that such bias was minimal but does not exclude the possibility of confounding by indication (for example, the prescribing of a drug to treat pain that may be a precursor of miscarriage). However, we cannot determine from our non-experimental data whether this association is causal or due to undetected confounding. Thus, in the case-control study we were not able to adjust for smoking status, as we did in the cohort study.

Apart from an unpublished study of use of ibuprofen in a cohort of 3,178 pregnant women from the Michigan Medicaid surveillance study,[18] we have not been able to identify any systematic studies of non-steroidal anti-inflammatory drug use in pregnant women. We have not found any studies of the association between non-steroidal anti-inflammatory drugs and miscarriage in humans. Because of the necessarily limited nature of studies of drug safety during pregnancy, it is important that all available data are combined to obtain the highest possible precision in the calculation of risk estimates. Our observation of an increased risk of miscarriage in women exposed to non-steroidal anti-inflammatory drug is new and needs to be confirmed.

Table 3.1 Comparison of pregnancies during which prescriptions for non-steroidal anti-inflammatory drugs were taken up and those during which no drugs were prescribed

Variable	Prescriptions taken up			No drug prescribed during pregnancy
	Between 30 days before conception and end of first trimester	In second and third trimester	Any time from 30 days before conception to term	
No of pregnancies	1106	997	1462	17 259
First pregnancies	449	381	576	9 263
Subsequent pregnancies	657	616	886	7 996
No of prescriptions	1257	1176	1742	—
Mean age (range) of mothers	28.1 (16-43)	28.3 (16-43)	28.3 (16-43)	28.5 (13-47)
No (%) of smokers	398 (36)	409 (41)	600 (41)	4 833 (28)
Gestational age:				
⩾37 weeks	1041	936	1374	16 268
34-6 weeks	41	40	59	682
<34 weeks	24	21	29	309
Mean weight (range) of babies at birth (grams)	3464 (639-5530)	3453 (639-5710)	3466 (639-5710)	3 483 (605-5 630)
No (%) of babies with birth defects	46 (4.2)	37 (3.7)	56 (3.8)	564 (3.3)
No (%) of preterm deliveries	65 (5.9)	61 (6.1)	88 (6.0)	991 (5.7)

Table 3.2 Logistic regression analyses of birth outcome in women who took up prescriptions for non-steroidal anti-inflammatory drugs during pregnancy and in women who were not prescribed any drug during pregnancy. Figures are crude and adjusted odds ratios (95% confidence intervals)

Variable	Birth defects		Low birth weight		Preterm delivery	
	Crude	Adjusted	Crude	Adjusted	Crude	Adjusted
Drugs:						
No drugs prescribed	1	1	1	1	1	1
Prescriptions taken up	1.29 (0.95-1.75)	1.27 (0.93-1.75)	0.84 (0.48-1.47)	0.79 (0.45-1.38)	1.07 (0.82-1.40)	1.05 (0.80-1.39)
Pregnancy:						
First	1	1	1	1	1	1
Subsequent	0.86 (0.73-1.01)	0.84 (0.70-1.01)	0.63 (0.50-0.81)	0.59 (0.45-0.77)	0.79 (0.69-0.89)	0.74 (0.64-0.85)
Smoking status:						
Non-smoker	1	1	1	1	1	1
Smoker	1.16 (0.97-1.39)	1.15 (0.96-1.38)	3.66 (2.86-4.67)	3.72 (2.90-4.77)	1.41 (1.23-1.61)	1.4 (1.23-1.61)
Maternal age:						
<25	1	1	1	1	1	1
25-30	0.89 (0.71-1.10)	0.93 (0.75-1.16)	0.68 (0.51-0.92)	0.93 (0.68-1.27)	0.85 (0.72-0.99)	0.88 (0.75-1.04)
>30	0.93 (0.76-1.15)	0.97 (0.76-1.23)	0.84 (0.63-1.14)	1.28 (0.92-1.79)	0.9 (0.77-1.07)	1.06 (0.88-1.27)

Table 3.3 Prescription of NSAIDs among women recorded as having a miscarriage in their first pregnancy compared with women who had a live birth (reference group). Figures are Number of pregnancies*

Variable	Miscarriage (n=4268)	Live birth (n=29 750)	Adjusted odds ratio (95% CI)
Time from taking up prescriptions for NSAIDs to date of discharge after miscarriage:			
1-12 weeks	63	318	1
1 week	3	9	6.99 (2.75 to 17.74)
2-3 weeks	5	15	3.00 (1.21 to 7.44)
4-6 weeks	14	41	4.38 (2.66 to 7.20)
7-9 weeks	19	92	2.69 (1.81 to 4.00)
10-12 weeks	22	161	1.26 (0.85 to 1.87)
Maternal age:			
<25 years (reference)	1022	8 284	1
25-29 years	1509	12 424	0.99 (0.91 to 1.07)
30-34 years	1128	6 728	1.36 (1.24 to 1.49)
>35 years	609	2 314	2.13 (1.91 to 2.38)
NSAIDs not prescribed during pregnancy	4205	29 432	

NSAIDs=non-steroidal anti-inflammatory drugs
*Only primigravidas are included in the analysis
The comparison period used for the reference group was the first trimester

Table 3.4 Birth defects recorded in women who took up prescriptions for non-steroidal anti-inflammatory drugs in the period from 30 days before conception to end of first trimester and in women who were not prescribed any drugs*

	ICD-8 code	ICD-10 code	No among women who took up prescriptions (n=1106)	No among women who were not prescribed drugs (n=17 259)
Malformations of the central nervous system:				
Spina bifida	741	53	1	11
Defect of spinal cord, non-specified		69	1	1
Malformation of nervous system, non-specified		78	1	6
Other			0	15
Facial malformations:				
Cataract		120	1	7
Atresia and stenosis of lacrimal duct	744.87		1	3
Malformation of face and neck, non-specified		188	1	13
Other			0	39
Cardiovascular malformations:				
Transposition of great vessels	746.19	203	2	4
Ventricular septal defect	746.39	210	4	48
Atrial septal defect	746.40	211	3	25
Atrio-ventricular septal defect		212	2	17
Malformation of heart, non-specified	746.89	249	4	41

Persistent ductus arteriosus	747.09	250	5	24
Coarctation of the aorta	474.19	251	4	6
Atresia of the pulmonary artery		255	1	1
Malformations of pulmonary veins		262	2	1
Other			0	24
Malformation of the respiratory system:				
Malformation of the larynx	748.30	314	2	1
Hypoplasia and dysplasia of lung		336	1	1
Other			0	17
Malformations of the palate:				
Unilateral palatoschisis		351	1	1
Other			0	36
Malformations of the digestive system:				
Ankyloglossia		381	1	8
Pylorospasm		400	1	26
Stenosis of colon		423	1	16
Annular pancreas		451	1	1
Other			0	11
Reproductive malformations:				
Hypospadias		541	1	46
Hydrocele testis	752.49		2	8
Other			0	12
Malformations of the urinary tract:				

Hydronephrosis		620	1	18
Posterior urethral valve		642	1	3
Malformation of urethra, non-specified		647	1	2
Other			0	15
Malformations of the locomotor system:				
Talipes equinovarus		660	2	56
Talipes calcaneovalgus		664	1	11
Other malformations of foot		668	3	4
Anomaly of face	756.00	674	1	7
Malformations of hand		681	1	30
Polydactyly		699	2	17
Syndactyly		709	1	30
Malformation of upper limb, non-specified		719	1	10
Malformation of lower limb, non-specified		728	1	15
Torticollis	756.81		1	6
Other malformations of muscle and bone		798	1	12
Naevus		825	1	17
Malformation, non-specified, non-classified	758.99	899	6	83
Other			0	126

*For each pregnancy there may have been more than one birth defect. Birth defects not occurring in the non-steroidal anti-inflammatory drugs cohort are grouped in the "Other" row for each group of malformations

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CHAPTER 4

Prenatal exposure to loratadine in children with hypospadias: A nested case-control study within the Danish National Birth Cohort

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INTRODUCTION

Hypospadias is a birth defect characterized by an urethral opening on the ventral side of the penis, as a result of abnormal urethral closure at 8 to 14 weeks gestation.1 It occurs with a reported prevalence of 0.3 to 0.8 percent for male live births and since the 1970s, multiple reports have shown an increase in the occurrence of hypospadias.[2-8] There is concern that this increase could result from increasing exposures to endocrine disruptor chemicals in the environment.[1] A variety of risk factors for hypospadias have been studied including, endocrine disrupters, gestational and pre-existing diabetes, intrauterine growth retardation, in vitro fertilization (IVF), maternal age, and genetic factors.[8-18]

Loratadine is a non-sedating antihistamine commonly used for seasonal allergies. It has a half-life of approximately 10 hours, but an effect on allergic reactions can still be detected at least 2 days after administration.[19]

In 2001, an increased risk of hypospadias associated with maternal use of loratadine was reported from Sweden, with a relative prevalence ratio of 2.39 (95% confidence interval [CI]: 1.43-3.38).[20] Since then, a number of studies have attempted to confirm this association. Both a small study from the Israeli Teratogen Information[21] and a similar small Canadian study showed no increased risk of birth defects among loratadine users.[22] Similarly, in a case-control study conducted by the American Centers of Disease Control and Prevention (CDC) there was no association between use of loratadine during pregnancy and hypospadias. However, this study did not include first-degree hypospadias.[23] Also a recent Danish registry-based case-control study found no association. [24]

However, the infrequent maternal use of loratadine in the critical period of pregnancy and the prevalence of hypospadias have a major impact on sample size requirements for providing the definitive assurances of the safety of loratadine to the unborn child.[25] There is especially a need for further studies with data on accurate timing on drug intake to explore the association between maternal exposure to loratadine and other anti-histamines and the risk of hypospadias, since both hypospadias and use of anti-allergic drugs is common, and any causal association may have public health implications. With this background, we conducted a nested case-control study within the Danish National Birth Cohort, which has information on timing, both for use of loratadine and other drugs, as well as on other potential confounders in the critical period of pregnancy.

MATERIALS AND METHODS

We examined the risk of hypospadias in a nested case-control design based on women enrolled in the Danish National Birth Cohort from 1998 to 2002. In 2002, the cohort comprised of approximately 95,000 pregnant women, which represents about 60% of the women invited to participate in the project.[26] Data on maternal use of medicine in pregnancy were retrieved from questionnaires and telephone interviews.[27] Outcome data were obtained from the National Hospital Discharge Registry (later named The Danish

National Registry of Patients) and linked to the Danish National Birth Cohort by means of the unique national registration number assigned to each resident of Denmark (CPR-number).

Data on use of loratadine and other exposures

At the first pregnancy examination at the GP (usually week 6-12 of gestation), before any prenatal test has been conducted, the women were asked to complete a questionnaire regarding use of medicine for the past three months. Therefore, in most cases, this questionnaire covered at least periconceptional use of medicine (30 days before conception) and early gestational use in pregnancy. Data on use of medicine later in pregnancy, not covered by the questionnaire, were collected by using detailed computerized telephone interviews. In total four interviews were scheduled to take place at around gestational weeks 12 and 30 (interviews 1 and 2) and when the child was six and 18 months old (interviews 3 and 4). In all interviews use of medicine was registered by the brand name and/or the drug code, and time of exposure was assigned in weeks of gestation (ranging from week 12 to week 40). From this registration, we identified users of loratadine, other antihistamines, IVF-drugs, antidiabetics and antiepileptics. Information about smoking, gestational age and birth order was similarly obtained from these interviews. We obtained information about preeclampsia from the National Danish Hospital Discharge Registry (ICD-10 codes O14 and O15).

Cases of hypospadias and other outcomes

From the National Danish Hospital Discharge Registry we identified all cases of hypospadias in the National Birth Cohort. A total of 203 cases of hypospadias, recorded within the first year postpartum, were identified between 1998 and 2002. The codes for hypospadias in ICD-10 codes are Q54.0 (hypospadias glandis, n=51), Q54.1 (hypospadias corporis penis, n=3), Q54.2 (hypospadias penoscrotalis, n=5), Q54.3 (hypospadias perinealis, n=1), Q54.4 (hypospadias penis arcuatos, n=5), Q54.8 (other specified hypospadias, n=2), Q54.9 (hypospadias without any specifications, n=59), (Children with multiple hypospadias codes, n=77). Data on other birth defects than hypospadias were not used in this study.

Controls

Within the National Birth Cohort we randomly selected 10 male controls per case matched by date of birth. The controls were selected when their corresponding case was diagnosed with hypospadias.

Statistical analysis

We classified the use of loratadine into two groups according to the time of exposure. The first group comprised of women exposed from 30 days before conception up to the end of the first trimester. The

second group comprised of those who were exposed to loratadine at any time during pregnancy. Users of other antihistamines were classified similarly.

We performed conditional logistic regression analyses to estimate the relative prevalence ratio – by virtue of the odds ratio - of hypospadias among users of loratadine compared with nonusers. By including use of other antihistamines, we were able to compare the risk of hypospadias among loratadine users versus other antihistamine users. We adjusted for the following variables in the analysis: maternal age (<25, 25-30, >30) birth order (1,1+), gestational age (<34 weeks, 34-36 weeks, ≥37 weeks), maternal smoking (yes, no or no information), reported use of ovulation-inducing drugs (yes, no), reported use of antiepileptics (yes, no), reported use of antidiabetics (yes, no), and preeclampsia (yes, no). Analyses were conducted separately for reported exposure within the first trimester or up to 30 days before conception and for reported exposure during the entire pregnancy or up to 30 days before conception.

All analyses were done using SAS version 8.02 (SAS Institute, NC, USA)

RESULTS

Approximately 95,000 women were included in the study cohort at the time of this nested case-control study.

Descriptive data for all 203 cases and 2,030 controls are shown in Table 4.1. One case (0.5 %) and 25 controls (1.2 %) reported exposure to loratadine compared with 4 cases (2.0 %) and 48 (2.4 %) controls to other antihistamines.

In total, 146 of the 203 cases were diagnosed with hypospadias within six months postpartum and none of these had reported exposure to loratadine during the entire pregnancy or up to 30 days before conception.

For exposure within the first trimester or up to 30 days before conception the adjusted odd ratio of loratadine exposure was 0.9 (95% CI: 0.1- 6.4) and the adjusted odds ratio for other antihistamines was 0.5 (95% CI: 0.1 – 1.9). For exposure within the entire pregnancy or up to 30 days before conception the adjusted odds ratio of loratadine exposure was 0.4 (95% CI: 0.1- 2.8) and adjusted odds ratio for other antihistamines was 0.7 (95% CI: 0.3 – 2.1) (Table 4.2).

DISCUSSION

We found no increased risk of hypospadias associated with use of either loratadine or any other antihistamine. However, the statistical precision of the risk estimates is low and, therefore, an association as the one found in the initial report of the Swedish Birth registry cannot be refuted entirely.[20]

Our study has strengths and limitations. We have complete and independent registration of birth and birth outcome. Because our case-control study was nested within a birth cohort the study population was well-defined and comparable, which made it possible to select an appropriate control group.

Data on exposure to loratadine and other antihistamines were self-reported and it is difficult to evaluate the recall accuracy for medications used in pregnancy. Only few studies have been published and there are substantial differences among these studies.[28] However, the period between use of loratadine and when it was reported was very short which may have improved accuracy. Compared with studies based on prescriptions it is a strength that self-reported data include information about loratadine bought "over-the-counter" (without prescription) and that they only include drugs which the women have actually taken (in contrast to merely dispensed as with a prescription database). We thus found the exposure rate among controls in the National Birth Cohort to be slightly higher than the exposure rate found in a recent Danish registry-based study (1.2% in our study versus 0.8% for the registry-based study). [24]

The fact that use of loratadine was reported antenatally reduces the risk of differential recall between cases and controls. Findings for example from case-control studies indicate that recall bias in studies of reproductive outcome tends to account for a higher reporting of potentially hazardous exposure after an adverse pregnancy outcome, and consequently overestimates the relative risk.[29]

The validity of the hypospadias diagnosis depends ultimately on the coding in the Danish Hospital Discharge Registry. It is known that discharge diagnoses may be incorrectly coded. However, a previous Danish study from one county found that the birth defect data were of high quality compared with those routinely collected in other countries; about 80-85% of diagnoses were correctly coded.[30] In addition, the estimated prevalence of hypospadias in our study corresponds to the prevalence reported in other datasets.

The Swedish study[20] which initially described that maternal use of loratadine was associated with an increased risk of hypospadias found that the risk was four-fold increased compared with maternal use of other anti-allergic anti-histamines. Although our data could not rule out an effect similar to the findings in this study, there were no suggestions of differences between the risk of hypospadias in users of loratadine and the risk in users of other antihistamines.

Our findings agree with the findings of both the recently conducted Danish registry-based study including 227 cases of hypospadias[24], as well as the study reported by CDC[23] which included 563 cases of second- or third-degree hypospadias. Similarly, in an Israeli study[21] of 210 pregnancies exposed to loratadine and 265 pregnancies exposed to other antihistamines there was no increased risk of hypospadias when compared to other antihistamines. The Canadian Multi center study,[22] which included 161 loratadine exposed pregnancies but did not include pregnancies exposed to other antihistamines, found no increased risk of hypospadias in the loratadine exposed group. Thus, the numbers of studies that fail to show an association between maternal loratadine use and hypospadias are increasing which suggests that the result found in the Swedish study[20] may have been due to chance or bias.

In conclusion, although the precision is low, these data do not indicate an increased risk of hypospadias associated with maternal exposure to loratadine. In addition, this study does not suggest any risk differential between maternal exposure to loratadine and other antihistamines.

Table 4.1 Characteristics of 203 cases of hypospadias (recorded within the first year postpartum) and 2030 control subjects

Variable	Cases N (%)	Controls N (%)
Exposure to loratadine*	1 (0.5)	25 (1.2)
30 days before conception and first trimester	1 (0.5)	12 (0.6)
Second trimester	0 (0.0)	8 (0.4)
Third trimester	0 (0.0)	13 (0.6)
Exposure to other antihistamines*	4 (2.0)	48 (2.4)
30 days before conception and first trimester	2 (1.0)	37 (1.8)
Second trimester	0 (0.0)	10 (0.5)
Third trimester	2 (1.0)	11 (0.5)
Maternal age		
<25	19 (9.4)	160 (7.9)
25-30	98 (48.3)	1,037 (51.1.6)
>30	86 (42.4)	833 (41.0)
Birth order		
1	115 (56.7)	900 (44.3)
1+	88 (43.3)	1,130 (55.7)
Smoking		
Yes	37 (18.2)	345 (17.0)
No	11 (5.4)	141 (7.0)
No information**	155 (76.4)	1 544 (76.1)
Gestational age		
≥37 weeks	167 (82.3)	1 982 (97.6)
34-36 weeks	23 (11.3)	41 (2.0)
<34 weeks	13 (6.4)	7 (0.3)
Exposure to ovulation-inducing drugs*	2 (1.0)	17 (0.8)
Exposure to antiepileptics*	1 (0.5)	5 (0.6)
Exposure to antidiabetics*	0 (0.0)	4 (0.2)
Preeclampsia	15 (7.4)	45 (2.2)

* Reported exposure during pregnancy or up to 30 days before conception
** Missing answer or 'not willing' to answer the question

Table 4.2 The association between hypospadias recorded anytime postpartum and maternal use of antihistamines, odds ratios (OR) and 95% confidence intervals (CI)

Variable	Crude OR (95% CI)	*Adjusted OR (95% CI)
Exposure 30 days before conception and first trimester :		
Loratadine	0.8 (0.1-6.4)	0.9 (0.1-6.9)
Other antihistamines	0.5 (0.1-2.2)	0.5 (0.1-1.9)
Exposure 30 days before conception and during pregnancy :		
Loratadine	0.4 (0.1-3.0)	0.4 (0.1-2.8)
Other antihistamines	0.8 (0.3-2.3)	0.7 (0.3-2.1)

*Adjusted for maternal age, maternal smoking, birth order, gestational age, preeclampsia, and use of ovulation-inducing drugs, antiepileptics, or antidiabetics

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CHAPTER 5

Maternal use of loratadine during pregnancy and risk of hypospadias in offspring

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INTRODUCTION

Hypospadias occurs with a reported prevalence of 0.3% to 0.8% and since the 1970s, multiple reports from the United States, England, Scandinavia, and Hungary have shown an increase in the occurrence of hypospadias.[1-7] Although very few risk factors for hypospadias are established, gestational and pre-existing diabetes, intrauterine growth retardation, paternal subfertility, *in vitro* fertilization (IVF), maternal age, and genetic factors have all been suggested to be associated with an increased risk of hypospadias.[8-17]

Loratadine is a non-sedating antihistamine commonly used for seasonal allergies.[18] In 2001, a report from Sweden suggested an association between maternal use of loratadine and infant hypospadias.[19] Having considered year of birth, maternal age, and parity, the odds ratio (OR) for hypospadias in relation to loratadine exposure was 2.39 (95% confidence interval [CI]: 1.43-3.38). The study also compared the occurrence of hypospadias after the use of other antihistamines. The OR for having a diagnosis of hypospadias in the Swedish Medical Birth Registry (MBR) after maternal use of loratadine compared with maternal use of other anti-allergic anti-histamines was 4.0 (95% CI:1.42-12.9).[19]

Neither a recent study from Israel including 210 pregnant women exposed to loratadine[20] nor a study that used data from four countries and included 161 pregnant women exposed to loratadine[21] found an increased risk of hypospadias. However, these studies had limited power and due to the low prevalence of hypospadias not one case could be expected. Recently, the American Centers of Disease Control and Prevention (CDC) reported a case-control study including 563 infants with second- or third-degree hypospadias.[22] This study did not find any association between loratadine use and hypospadias. But since first-degrees hypospadias was excluded CDC could not assess the potential association between the mildest form of hypospadias and loratadine. Since use of anti-allergic drugs is common, any causal association may have major public health implications. We, therefore, conducted a case-control study in Denmark based on hospital discharge data of cases with hypospadias and population controls linked to Danish prescription registries.

MATERIALS AND METHODS

Study population

The study was conducted in the four Danish counties of North Jutland, Aarhus, Viborg and Ringkjøbing which account for 30% of the Danish population (~1.6 M). A total of 65,383 male births with a full prescription history of the mother were available for analyses in the study period from 1989-2002 (North Jutland n=34,859), 1996-2002 (Aarhus n=20,382) and 1998-2002 (Viborg n=4,148) and (Ringkjøbing n=5,994).

Cases of hypospadias

We identified all cases of hypospadias in the period 1989-2003 from the nationwide Hospital Discharge Registry (HDR). This Registry comprises of data on all discharges from hospitals in Denmark and includes 10-digit personal identifiers, dates of admission and discharge, surgical procedures, and up to 20 diagnoses[23] classified according to the Danish versions of the International Classification of Diseases, 8th Revision (ICD-8) until the end of 1993 and ICD-10 thereafter (ICD-9 was never used in Denmark). The codes for hypospadias in ICD-8 are 752.20 (hypospadias glandis, n=3), 752.21 (hypospadias corporis penis, n=1), 752.22 (hypospadias scrotalis, n=0), 752.28 (hypospadias alia definite, n=0), 752.29 (hypospadias, n=5); in ICD-10, the codes are Q54.0 (hypospadias glandis, n=101), Q54.1 (hypospadias corporis penis, n=11), Q54.2 (hypospadias penoscrotalis, n=0), Q54.3 (hypospadias perinealis, n=2), Q54.4 (hypospadias penis arcuatos, n=3), Q54.8 (other specified hypospadias, n=0), Q54.9 (hypospadias without any specifications, n=135); There were 159 children with multiple hypospadias codes, and 25 children with both ICD-8 and ICD-10 codes. Using these codes, a total of 319 cases of hypospadias were identified (anytime postpartum) in the cohort of 65,383 male births in the four counties.

The Danish Medical Birth Registry

The MBR, which comprises of data collected by midwives and doctors attending deliveries, contains information on all births in Denmark since 1 January 1973.[24,25] The main data constitute maternal age, self-reported smoking status at first antenatal visit, birth order, stillbirth, Apgar score, gestational age, height and weight of the neonate, and personal identifiers for both mother and child.[24]

Use of loratadine, other antihistamines, IVF drugs, antidiabetics and epileptics

As a part of the tax-funded healthcare for all inhabitants, the Danish National Health Service reimburses part of the patient expenditure on a wide range of prescribed drugs[21,26] Danish patients are served by pharmacies equipped with electronic accounting systems that are used primarily to secure reimbursement for the National Health Service in each county. These systems include information on WHO's Anatomical Therapeutic Chemical (ATC) classification code, the amount of the drug prescribed, the personal identification number, and the date of drug dispension. Since January 1 1989 all data from North Jutland County have been stored in a prescription database maintained by the Department of Clinical Epidemiology, Aarhus University Hospital and since 2000 the Department of Clinical Epidemiology has also maintained similar research prescription databases from the three other counties. The data from these three counties are available from January 1, 1996 (Aarhus County) and January 1, 1998 (Ringkjøbing and Viborg counties). Drugs sold over the counter are not available in these Prescriptions databases

Among cases and controls, prescriptions on loratadine (ATC codes: R06AX13), other antihistamines (ATC code: R06, except R06AX13), clomifene (ATC code: G03GB02), antidiabetics (ATC code: A10) and epileptics (ATC code: N03) was obtained from the prescription databases.

Data on preeclampsia

From the HDR we also obtained information on preeclampsia (ICD-8 codes: 637.03, 637.04, 637.09, 637.19; ICD-10 codes: 014, 015), since this has been found to be associated with hypospadias. The unique personal identifiers (CPR-numbers) were used to link records from all registries.

Statistical analysis

The association between use of loratadine and hypospadias was studied in a nested case-control design within the cohort of women who had a livebirth or a stillbirth after the 28th week of gestation. Use of loratadine was classified into three groups according to the time of exposure. The first trimester is considered the critical period for organ formation. Thus, the primary focus was the "early pregnancy" group, comprising of women who filled a prescription within 30 days before conception ("conception" was defined as the first day of last menstrual period [LMP]) up to the end of the first trimester (week 14 after the LMP). A second group comprised of women who filled a prescription within the first six months of pregnancy. A third group, the "entire pregnancy" group, comprised of women who filled prescriptions for loratadine at any time during pregnancy. Users of other antihistamines were classified similarly.

We restricted the first analysis to the pregnancies where the women lived in the four counties during the complete study period, which was the period between 30 days before conception and six months post-delivery. In the first analysis, cases were defined as boys with hypospadias recorded in the HDR during the first six months post-delivery.

The controls were selected from the study population of 65,383 male births. The control group comprised of 10 controls per case, and these controls had no recorded diagnosis of hypospadias during the first six months post delivery. We matched on birth, month, and year of the child. To examine whether the restriction of the hypospadias diagnosis to six months post-delivery had any impact on the results, we conducted a second analysis in which we defined cases as boys with hypospadias recorded in the HDR any time post-delivery (some children might have been coded later e.g. at the time of surgery) and controls as boys with no recorded diagnosis of hypospadias during the study period. In this analysis, cases and controls had to have lived in the four counties until the cases were diagnosed.

For the main study variables, we constructed contingency tables between exposure to loratadine, other antihistamines, case/control status and possible confounders. We used exact conditional logistic

regression to estimate the relative risk by virtue of the OR of hypospadias associated with exposure to loratadine adjusted for maternal age, birth order, smoking status, preeclampsia, use of clomifene (a proxy for IVF), diabetes, and epilepsy. The analyses were done using SAS version 9.1 (SAS Inc., Cary, NC, USA).

RESULTS

We identified 227 cases of hypospadias and 2270 matched controls when considering diagnosis within six months postpartum. Descriptive data for cases and controls are shown in Table 5.1. A total of one case and eight controls were exposed to loratadine in the first trimester or up to 30 days before the time of conception compared with four cases and 23 controls exposed to other antihistamines in the first trimester or up to 30 days before the time of conception.

Table 5.2 shows the ORs for hypospadias associated with exposure to loratadine and other antihistamines according to the time of exposure. The adjusted OR for loratadine exposure within 30 days before conception and during the first trimester was 1.4 (95% CI: 0.0-10.5). The adjusted OR for other antihistamines was 1.9 (95% CI: 0.5-5.8). The crude and adjusted odds ratios were similar, suggesting that the variables we controlled for were no major confounders.

For the second group, who filled the prescription within the first six month of pregnancy, and the third, "entire pregnancy" group, the adjusted ORs for loratadine exposure were 0.8 (95% CI: 0.0-4.9) and 0.5 (95% CI: 0.0-3.3), respectively. The adjusted ORs for other antihistamines were 1.6 (95% CI: 0.3-5.5) and 1.0 (95% CI: 0.2-3.4), respectively.

Considering all cases of hypospadias recorded anytime post-delivery (*N*=319), the risk estimates did not change markedly. The adjusted OR for exposure to loratadine in the first trimester and 30 days before conception was 1.1 (95% CI: 0.0-7.7), and the OR for exposure to other antihistamines in the same period was 1.7 (95% CI: 0.5-4.7). The adjusted OR for exposure to loratadine within the first six months of pregnancy was 0.6 (95% CI 0.0-3.8) and for the entire pregnancy 0.5 (95% CI 0.0-2.7). The adjusted ORs for other antihistamines were 1.1 (95% CI: 0.2-3.7) and 0.7 (95% CI: 0.1-2.3), respectively. The risk point estimates were generally higher for other antihistamines than for loratadine.

Since we only had one exposed case, our dataset did not allow separate analyses of hypospadias as a single outcome or as an outcome in combination with other birth defects. Such an analysis might have been useful in order to examine the presence of surveillance bias, as hypospadias occur in clusters with other birth defects in some children.

DISCUSSION

The current study has shown that maternal exposure to loratadine does not appear to be associated with an increased risk of hypospadias compared with other antihistamines. In fact, the risk point estimates for hypospadias were higher with maternal exposure to other antihistamines compared with loratadine. Thus, our risk estimates do not corroborate the findings in the Swedish study[19] that initiated the hypospadias debate. However our risk estimates had limited statistical precision and an effect similar to that in the Swedish study cannot be ruled out entirely.

Our case-control study had complete and independent registration of birth, birth outcome, and prescription data which prevented selection bias and some types of information bias; since the study was based on routinely recorded data, independent of the diagnosis, Importantly, there was no risk of recall bias, which can invalidate case-control studies that solely rely on interviews. [27] Although smaller than the Swedish Birth Registry, the database we used is one of the largest in the world for studying the safety of drugs used in pregnancy and previous studies have shown high data quality in both the prescription database and the Birth Registry.[25,28] Coding errors occur in less than 0.5 percent of cases in the prescription database.[28]

Our study was based on the HDR, and it is known that discharge diagnoses listed in discharge registries are not always accurate. We reviewed 43 records of the hypospadias cases in our study and found only three to be misclassified. Generally, lack of specificity, biases risk estimates towards unity. However, our prevalence of hypospadias corresponds to the prevalence reported in other datasets.

Loratadine is also sold "over the counter" in Denmark and since the prescription databases do not capture information regarding "over the counter" medication, the exposure information may be incomplete. Incomplete exposure information in the current study may bias the results towards unity as well.

Because of our reliance on dispensing information in the record linkage study, we do not know whether the women in the study actually took the drugs. However, the fact that patients are required to pay partially for the costs themselves is likely to have improved compliance.

We were able to adjust for possible confounding factors except for the years 1989 and 1990, where we did not have information regarding smoking. However, in our study, adjustment for the available confounding variables did not change the unadjusted risk estimates substantially, implying that these variables were no major confounders. Since the development of the external organs is initiated in the early fetal period, some of the studied variables such as preeclampsia should be interpreted as biological characterization of infants born with hypospadias rather than possible causal factors.

Our data are in line with the few other existing studies. Thus, in a recently conducted study by the CDC no association between maternal use of loratadine and second- or third-degree hypospadias was demonstrated.[22] Similarly, in an Israeli study,[20] no increased risk of hypospadias was demonstrated in the loratadine group compared with other antihistamines. Moretti and coworkers found in a multi center study[21] that maternal exposure to loratadine was not associated with major birth defects.

However, the infrequent maternal use of loratadine and the prevalence of hypospadias have a major impact on sample size requirements for providing the definitive assurances of the safety of loratadine to the unborn child.[29] Thus, to rule out a doubling of the risk of hypospadias would, based on our registries, require a study with 1,350 cases of hypospadias and 13,500 controls (power 80 percent and 0.5% exposure prevalence among controls).

CONCLUSION

In conclusion, maternal exposure to loratadine does not appear to be associated with an increased risk of hypospadias compared to other antihistamines However, the statistical precision of our risk estimates was limited.

Table 5.1 Characteristics of 227 cases of hypospadias recorded within six months postpartum and 2270 control subjects.

Variable	Cases *N* (%)	Controls *N* (%)
Exposure to Loratadine*	1 (0.4)	22 (1.0)
30 days before conception and first trimester	1 (0.4)	8 (0.4)
First trimester and second trimester	1 (0.4)	15 (0.7)
During pregnancy	1 (0.4)	21 (0.9)
Exposure to other antihistamines*	4 (1.8)	40 (1.8)
30 days before conception and first trimester	4 (1.8)	23 (1.0)
First trimester and second trimester	3 (1.3)	21 (0.9)
During pregnancy	3 (1.3)	30 (1.3)
Maternal age		
<25	41 (18.1)	319 (14.1)
25-30	99 (43.6)	1,036 (45.6)
>30	87 (38.3)	915 (40.3)
Birth order		
1	108 (47.6)	942 (41.5)
1+	119 (52.4)	1,328 (58.5)
Smoking 1991-2002		
Yes	51 (22.5)	524 (23.1)
No	156 (68.7)	1,571 (69.2)
Missing	20 (8.8)	175 (7.7)
Gestational age		
≥37 weeks	198 (87.2)	2,160 (95.2)
34-36 weeks	20 (8.8)	81 (3.6)
<34 weeks	9 (4.0)	29 (1.3)
Prescription for ovulation-inducing drugs	1 (0.4)	44 (1.9)
Maternal epilepsy	2 (0.9)	13 (0.6)
Maternal diabetes	1 (0.4)	8 (0.4)
Preeclampsia	13 (5.7)	48 (2.1)

*Exposure during pregnancy and 30 days before conception

Table 5.2 The association between hypospadias recorded within six months postpartum and maternal use of antihistamines according to time of exposure, odds ratios (OR) and 95% confidence intervals (CI)

Time of exposure	**Crude OR (95% CI)**	***Adjusted OR (95% CI) 1989-2002**	****Adjusted OR (95% CI) 1991-2002**
Exposure 30 days before conception and first trimester :			
Loratadine	1.3 (0.0-9.3)	1.4 (0.0-10.6)	1.4 (0.0-10.5)
Other antihistamines	1.7 (0.4-5.2)	1.8 (0.4-5.3)	1.9 (0.5-5.8)
Exposure first and second trimester :			
Loratadine	0.7 (0.0-4.4)	0.7 (0.0-4.8)	0.8 (0.0-4.9)
Other antihistamines	1.4 (0.3-4.9)	1.4 (0.3-4.9)	1.6 (0.3-5.5)
Exposure during pregnancy :			
Loratadine	0.5 (0.0-3.0)	0.5 (0.0-3.2)	0.5 (0.0-3.3)
Other antihistamines	1.0 (0.2-3.3)	1.0 (0.2-3.3)	1.0 (0.2-3.4)

*Adjusted for maternal age, birth order, ovulation-inducing drugs, maternal epilepsy, maternal diabetes and preeclampsia.
**Adjusted for smoking, maternal age, birth order, ovulation-inducing drugs, maternal epilepsy, maternal diabetes and preeclampsia.

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CHAPTER 6

Maternal use of loratadine during pregnancy and prevalence of hypospadias in offspring: A Danish nationwide case-control study

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INTRODUCTION

Hypospadias is a common birth defect, characterized by an incomplete development of the anterior urethra and with clinical complications stemming from poor control of the urinary stream, infertility, and psychological stress. It has been suggested that changes in concentrations of sex hormones during the fetal critical period of genital development (weeks 8-14) may play a role in the development of hypospadias. Gestational and pre-existing diabetes, intrauterine growth retardation, paternal subfertility, in vitro fertilization, maternal age, genetic factors and environmental chemicals have all been reported to be associated with an increased prevalence of hypospadias.[1-15]

Hypospadias occurs with a reported prevalence of 0.3 to 0.8 percent of births. Since the 1970s, multiple reports from several countries have shown an increase in the prevalence of hypospadias,[1-4] but the reasons behind the increasing prevalence remain largely unknown.

The Swedish Medical Birth Registry is used for monitoring drug use in early pregnancy and the occurrence of birth defects in infants.[16] In 1997, an association was noted between hypospadias and maternal use of the anti-allergic drug loratadine. Continued monitoring suggested that the association was not readily consistent with a chance explanation. In November 2001, 2,780 exposed infants were identified in the registry, among whom there were 15 cases of hypospadias, compared with 5.6 cases expected based on a population rate of one case per 500 in the general population. The adjusted odds ratio for hypospadias and loratadine exposure was 2.39 (95 percent confidence interval, 1.43 to 3.38). The study also compared the occurrence of hypospadias after the use of other anti-allergic drugs; among 5,116 infants exposed to such drugs, six had hypospadias (expected number 10.2), and the odds ratio for having a diagnosis of hypospadias in the Medical Birth Registry after maternal use of loratadine, compared with maternal use of other anti-allergic anti-histamines, was 4.0 (95 percent confidence interval, 1.42 to 12.9).[16]

Recently, the Swedish group repeated the analysis for the period 2002-2004 and reported a prevalence ratio of 0.47 (95 percent confidence interval, 0.06 to 1.65), a value considerably different from their earlier report. This newer analysis was based on 1,911 infants exposed to loratadine in early pregnancy.[17] Other attempts to clarify these issues have been hampered by insufficient data and inconsistent results.[18-23]

Since use of anti-allergic drugs is common, any causal association may have major public health implications. To examine this issue, we conducted a large nationwide case-control study in Denmark, based on administrative medical health databases and linkage to the Danish nationwide prescription database.

SUBJECTS AND METHODS

Cases of hypospadias

We identified all boys with hypospadias in Denmark born in the period 1996-2004 from the nationwide Hospital Discharge Registry (HDR).23 Since almost no private inpatient treatment exists in Denmark, this Registry comprises data on all discharges from hospitals in Denmark and includes 10-digit personal identifiers, dates of admission and discharge, surgical procedures, and up to 20 diagnoses23 classified according to the Danish versions of the International Classification of Diseases, 8th Revision (ICD-8) until the end of 1993 and ICD-10 thereafter (ICD-9 was never used in Denmark). The codes for hypospadias in ICD-10 are Q54.0 (hypospadias glandis, n=640), Q54.1 (hypospadias corporis penis, n=173), Q54.2 (hypospadias penoscrotalis, n=41), Q54.3 (hypospadias perinealis, n=9), Q54.4 (hypospadias penis arcuatos, n=48), Q54.8 (other specified hypospadias, n=10), Q54.9 (hypospadias without any specifications, n=654). Using these codes, a total of 1575 cases of hypospadias were identified anytime post-delivery and 1081 cases of hypospadias within 6 month post-delivery.

The Danish Medical Birth Registry

The Danish Medical Birth Registry, which comprises data collected by midwives and doctors attending deliveries, contains information on all births in Denmark since January 1, 1973.[24-26] The main data constitute maternal age, self-reported smoking status at first antenatal visit, birth order, stillbirth, Apgar score, gestational age, height and weight of the neonate, and personal identifiers for both mother and child.[24]

Selection of controls

Using the DMBR we randomly selected up to 10 controls (live male births) for each case without a diagnosis of hypospadias and matched by birth year and mother's residence.[26,27] We could not find 10 eligible matches for all cases. On average we found 9.3 matching controls; 1,572 (99.8%) cases had at least five eligible matched controls. There were a total of 14,660 controls.

Use of antihistamines, clomifene, antidiabetics and antiepileptics

Since January 1, 1995, prescriptions have been stored in a nationwide prescription database maintained by The Danish Medicines Agency.[28] The database retains key information for all refundable drugs dispensed from all pharmacies in Denmark. This information includes the civil registry number of patients, type of drug prescribed according to the anatomical therapeutical chemical (ATC) classification system, and date of prescription. Through the prescription database we identified all maternal prescriptions before the birth date for loratadine (ATC codes: R06AX13), other antihistamines (ATC

code: R06, except R06AX13), clomifene (ATC code: G03GB02), antidiabetics (ATC code: A10) and antiepileptics (ATC code: N03).

Data on preeclampsia

From the Hospital Discharge Registry we also obtained information on maternal preeclampsia (ICD-10 codes: 014, 015), as this condition has been found to be associated with hypospadias.[29]

Record linkage

The unique personal identifiers were used to link records from all registries.[27]

Statistical analysis

Use of loratadine was classified into three groups according to the time of exposure. The first trimester is considered the critical period for formation of the urethra. Thus, the primary focus was the "early pregnancy" exposure group, comprising women who filled a prescription within the interval beginning 30 days before conception ("conception" was defined as the first day of last menstrual period) and ending at week 14 after the last menstrual period. A second, broader definition of exposure was the group of women who filled a prescription within the first six months of pregnancy. A third group, the "entire pregnancy" group, comprised women who filled prescriptions for loratadine at any time during pregnancy. Users of other antihistamines were classified similarly.

In the first analysis, cases were defined as boys with hypospadias recorded in the Hospital Discharge Registry any time post-delivery and controls as boys with no recorded diagnosis of hypospadias during the study period.

To examine whether the time of the hypospadias diagnosis had any influence on the results (as some children might have been assigned codes later, for example at the time of surgery), we conducted a second analysis in which we defined cases as boys with hypospadias that was recorded in the Hospital Discharge Registry within six months of being born.

For the main study variables, we constructed contingency tables between exposure to loratadine, other antihistamines, case/control status and possible confounders. We used conditional logistic regression to estimate the prevalence ratio (estimated from the prevalence odds ratio) of hypospadias associated with exposure to loratadine and other antihistamines adjusted for potential confounding factors, including maternal age, smoking status, birth order, preeclampsia, prescription for clomifene, antidiabetics or antiepileptics.

The analyses were performed using SAS version 9.1 (SAS Inc., Cary, NC, USA).

RESULTS

We identified 1,575 cases of hypospadias recorded anytime post-delivery and 14,660 controls. Of these 1,081 cases of hypospadias were recorded within six months post-delivery, and 10,049 controls were matched to those cases. Descriptive data for these cases and controls are shown in Table 6.1 and 6.2. None of the loratadine exposed cases of hypospadias occurred in combination with other birth defects.

A total of seven cases (0.4 percent) and 88 controls (0.6 percent) were exposed to loratadine in the first trimester or up to 30 days before the time of conception. There were 28 cases (1.8 percent) and 217 controls (1.5 percent) exposed to other antihistamines in the first trimester or up to 30 days before the time of conception.

Table 6.3 shows the prevalence ratios for hypospadias associated with exposure to loratadine and other antihistamines according to the time of exposure and according to the time of recorded diagnosis post-delivery.

Considering all cases of hypospadias recorded anytime post-delivery (N=1,575), the adjusted prevalence ratio for exposure to loratadine in the first trimester and 30 days before conception was 0.6 (95 percent confidence interval, 0.3 to 1.4), and the prevalence ratio for exposure to other antihistamines in the same period was 1.3 (95 percent confidence interval, 0.9 to 1.9). The unadjusted and adjusted prevalence ratios were similar, suggesting that there was no important confounding among the set of variables that we controlled.

For the second group, who filled the prescription within the first six month of pregnancy, and the third, "entire pregnancy" group, the adjusted prevalence ratios for loratadine exposure were 1.0 (95 percent confidence interval, 0.6 to 1.9) and for the entire pregnancy 0.9 (95 percent confidence interval, 0.5 to 1.6). The adjusted prevalence ratios for other antihistamines were 1.3 (95 percent confidence interval, 0.9 to 1.9) and 1.0 (95 percent confidence interval, 0.7 to 1.5), respectively. The point estimates were generally higher for other antihistamines than for loratadine.

For cases recorded within 6 month post-delivery, the prevalence ratio estimates did not change markedly. The adjusted prevalence ratio for loratadine exposure within 30 days before conception and during the first trimester was 0.6 (95 percent confidence interval, 0.2 to 1.7). The corresponding adjusted prevalence ratio for other antihistamines was 1.1 (95 percent confidence interval, 0.6 to 1.8). The adjusted prevalence ratio for exposure to loratadine within the first six month of pregnancy was 1.0 (95 percent confidence interval, 0.5 to 2.1) and for the entire pregnancy 0.9 (95 percent confidence interval, 0.5 to 1.8). The

corresponding adjusted prevalence ratios for other antihistamines were 1.2 (95 percent confidence interval, 0.7 to 1.9) and 1.0 (95 percent confidence interval, 0.7 to 1.6), respectively.

DISCUSSION

In this large population based nationwide study we found that maternal exposure to loratadine had a negative association with hypospadias, with a prevalence ratio of 0.6 for first trimester exposure. In contrast, the association for maternal exposure to other antihistamines was positive, with a prevalence ration of 1.3. These results do not corroborate the early findings in the Swedish study16 that initiated the hypospadias debate, but are consistent with the other small studies that have reported on this topic.[18-22]

In a recently conducted study by the American Centers for Disease Control and Prevention (CDC) that included 563 infants with second- or third-degree hypospadias, the adjusted odds ratio for hypospadias and maternal use of loratadine was 0.96 (95 percent confidence interval, 0.4 to 2.2).[20] Both an Israeli study of 210 loratadine exposed pregnancies 18 and a Canadian study of 161 loratadine exposed pregnancies19 identified no cases of hypospadias among exposed infants.

Neither a Danish study[22] based on self-reported use of medicine in pregnancy that included 202 cases of hypospadias, nor a register-based case-control study in four Danish counties that included 319 cases of hypospadias[21] found an increase in prevalence of hypospadias among users of loratadine (adjusted odds ratios were 0.9 (95 percent confidence interval 0.1 to 6.9) and 1.4 (95 percent confidence interval 0.0-11.2), respectively).

Although our study has the strength of large size and complete and independent registration of birth and birth outcome, the validity of our estimates depends on the accurate coding of hypospadias and of the quality of the prescription data. Discharge diagnoses listed in discharge registries are not always perfectly accurate. In an earlier study we have reported the predictive value of the hypospadias codes to be 95 percent. This imperfect specificity in routinely recorded data is most likely independent of prescription information and would therefore bias the prevalence ratio estimates towards unity. As we found a prevalence ratio estimate considerably below unity, this source of bias is not likely to be masking a real positive effect in our data.

Because we used prescription data, there is no risk of recall bias, which can affect case-control studies of maternal drug use that rely solely on interviews.[30] Loratadine is also sold "over the counter" in Denmark and since the prescription database does not capture information regarding "over the counter" medication, the exposure information in our study is incomplete. The reported exposure proportion in this study is similar to the findings of the Danish study that used self-reported data[22], implying that over the counter

use of loratadine is not substantial, although both studies could be in error for different reasons. Incomplete exposure information would bias the results towards unity and therefore would not be likely to be masking a real positive effect.

Because of our reliance on medical databases, we do not know whether the women in the study actually took the drugs. Patients are required to pay part of the costs of their medication, however, which may result in high use among those filling prescriptions. Any misclassification resulting from nonuse of the prescribed medication is presumably similar for cases and controls; such nondifferential misclassification would bias the prevalence ratio toward unity. To the extent misclassification is an issue, it presumably would affect other antihistamine use to the same extent as loratadine.

CONCLUSION

Maternal exposure to loratadine was negatively associated with hypospadias in our data, in the opposite direction to the association for other antihistamines.

Table 6.3 Characteristics of 1575 cases of hypospadias recorded anytime post-delivery and 14,660 control subjects

Variable	Cases N (%)	Controls N (%)
Exposure to loratadine*	15 (1.0)	171 (1.2)
30 days before conception and first trimester	7 (0.4)	88 (0.6)
First trimester and second trimester	13 (0.8)	113 (0.8)
During pregnancy	15 (1.0)	148 (1.0)
Exposure to other antihistamines*	45 (2.9)	401 (2.7)
30 days before conception and first trimester	28 (1.8)	217 (1.5)
First trimester and second trimester	32 (2.0)	246 (1.7)
During pregnancy	36 (2.3)	345 (2.4)
Maternal age		
<25	246 (15.6)	2228 (15.2)
25-30	560 (35.6)	5299 (36.2)
>30	769 (48.8)	7133 (48.7)
Birth order		
1	716 (45.5)	6175 (42.1)
1+	811 (51.5)	8134 (55.5)
Missing	48 (3.1)	351 (2.4)
Smoking		
Yes	307 (19.5)	3151 (21.5)
No	1179 (74.9)	10,892 (74.3)
Missing	89 (5.7)	617 (4.2)
Marital status		
Married	843 (53.5)	7996 (54.5)
Otherwise	731 (46.4)	6661 (45.4)
Missing	1 (0.1)	3 (0.0)
Gestational age		
≥37 weeks	1372 (87.1)	13,819 (94.3)
34-36 weeks	114 (7.2)	550 (3.8)
<34 weeks	71 (4.5)	217 (1.5)
Missing	18 (1.1)	74 (0.5)
Apgar score at 5 min.		

< 7	26 (1.7)	137 (0.9)
≥ 7	1521 (96.6)	14,357 (97.9)
Missing	28 (1.8)	166 (1.1)
Antenatal examinations (median, range)		
At the midwife clinic	5 (0-16)	6 (0-25)
At the GP	3 (0-9)	3 (0-9)
With a specialist	1 (0-9)	1 (0-9)
Exposure to ovulation-inducing drugs#	59 (3.8)	378 (2.6)
Exposure to antiepileptics§	19 (1.2)	156 (1.1)
Exposure to antidiabetics§	12 (0.8)	71 (0.5)
Preeclampsia	75 (4.8)	365 (2.5)

*At least one prescription reimbursed during pregnancy and up to 30 days before conception.
#At least one prescription reimbursed in first trimester and up to 90 days before conception.
§At least one prescription reimbursed during pregnancy or anytime before conception

Table 6.2 Characteristics of 1081 cases of hypospadias recorded within 6 month post-delivery and 10,049 control subjects

Variable	Cases N (%)	Controls N (%)
Exposure to loratadine*	11 (1.0)	129 (1.3)
30 days before conception and first trimester	4 (0.4)	58 (0.6)
First trimester and second trimester	9 (0.8)	84 (0.8)
During pregnancy	11 (1.0)	114 (1.1)
Exposure to other antihistamines*		
	27 (2.5)	280 (2.8)
30 days before conception and first trimester	16 (1.5)	151 (1.5)
First trimester and second trimester	20 (1.9)	174 (1.7)
During pregnancy	23 (2.1)	238 (2.4)
Maternal age		
<25	173 (16.0)	1526 (15.2)
25-30	385 (35.6)	3630 (36.1)
>30	523 (48.4)	4893 (48.7)
Birth order		
1	488 (45.1)	4167 (41.5)
1+	569 (52.6)	5676 (46.5)
Missing	24 (2.2)	206 (2.1)
Smoking		
Yes	214 (19.8)	2185 (21.7)
No	804 (74.4)	7,468 (74.3)
Missing	63 (5.8)	396 (3.9)
Marital status		
Married	587 (54.3)	5469 (54.4)
Otherwise	494 (45.7)	4580 (45.6)
Missing	0 (0.0)	0 (0.0)
Gestational age		
≥37 weeks	926 (85.7)	9,483 (94.4)
34-36 weeks	86 (8.0)	380 (3.8)
<34 weeks	57 (5.3)	138 (1.4)
Missing	12 (1.1)	48 (0.5)
Apgar score at 5 min.		

< 7	21 (1.9)	92 (0.9)
≥ 7	1040 (96.2)	9,850 (98.0)
Missing	20 (1.9)	107 (1.1)
Antenatal examinations (median, range)		
At the midwife clinic	5 (0-16)	6 (0-25)
At the GP	3 (0-9)	3 (0-9)
With a specialist	1 (0-9)	1 (0-9)
Exposure to ovulation-inducing drugs#	43 (4.0)	254 (2.5)
Exposure to antiepileptics§	14 (1.3)	108 (1.1)
Exposure to antidiabetics§	12 (1.1)	44 (0.4)
Preeclampsia	58 (5.4)	252 (2.5)

*At least one prescription reimbursed during pregnancy and up to 30 days before conception
#At least one prescription reimbursed in first trimester and up to 90 days before conception
§At least one prescription reimbursed during pregnancy or anytime before conception

Table 6.3 The association between hypospadias and maternal use of antihistamines according to time of exposure, prevalence ratios (PR) and 95% confidence intervals (CI)

Time of exposure	Hypospadias recorded within six months post-delivery		Hypospadias recorded anytime post-delivery	
	Unadjusted PR (95% CI)	*Adjusted PR (95% CI)	Unadjusted PR (95% CI)	*Adjusted PR (95% CI)
Exposure 30 days before conception and first trimester :				
Loratadine	0.6 (0.2-1.7)	0.6 (0.2-1.7)	0.7 (0.3-1.6)	0.6 (0.3-1.4)
Other antihistamines	1.0 (0.6-1.7)	1.1 (0.6-1.8)	1.2 (0.8-1.8)	1.3 (0.9-1.9)
Exposure first and second trimester :				
Loratadine	1.0 (0.5-2.0)	1.0 (0.5-2.1)	1.1 (0.6-1.9)	1.0 (0.6-1.9)
Other antihistamines	1.1 (0.7-1.7)	1.2 (0.7-1.9)	1.2 (0.8-1.8)	1.3 (0.9-1.9)
Exposure during pregnancy :				
Loratadine	0.9 (0.5-1.7)	0.9 (0.5-1.8)	0.9 (0.5-1.6)	0.9 (0.5-1.6)
Other antihistamines	0.9 (0.6-1.4)	1.0 (0.7-1.6)	1.0 (0.7-1.4)	1.0 (0.7-1.5)

* Adjusted for including maternal age, smoking status, birth order, preeclampsia, prescription for IVF, Antidiabetics or Antiepileptics

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CHAPTER 7

Conclusion and perspectives

The following conclusions can be drawn from the thesis:

1. Danish health care databases have a unique potential for large studies of drug-induced birth defects. A comprehensive system of linkable Danish data allows for studies of low cost with long and complete follow-up, with the possibility to monitor the morbidity in children exposed in utero. The data allow for case-control designs, case-time-control designs and cohort designs. The validity of the study results relies on the quality of discharge diagnoses and prescription data. Therefore information bias, selection bias and confounding should be understood and effectively dealt with in order to conduct quality studies of drug-induced birth defects.

2. Based on Danish registries and prescription databases, we found no increased risk of preterm birth, low birth weight or birth defects among pregnant women exposed to NSAIDs in the period from 30 days before conception until end of pregnancy. However, exposure of NSAIDs was associated with an increased risk of spontaneous abortion.

3. In a study based on women enrolled in the Danish National Birth Cohort, we did not find an association of self-reported anti-allergic drug use in pregnancy and the risk of hypospadias. In addition, in two Danish studies based on prescription databases, we did not find any increased risk of anti-allergic drug use in pregnancy and the risk of hypospadias. None of the three studies of anti-allergic drugs suggested any risk differential between exposure to loratadine and other anti-allergic drugs.

In this thesis, several methodological considerations have been raised in studies of drug-induced birth defect. Drugs are taken by more than half of all pregnant women in the developed world[1,2] and probably a small fraction of these drugs have unknown short- or long-term consequences for the offspring.[3,4] With a few exceptions, we are ignorant of the biologic mechanisms by which most human birth defects occur. Moreover, indirect fetal benefits or risks associated with maternal drug intake or influence of the drug exerted on the fetus alone are not well understood.[5] Consequently, this ignorance makes it difficult to determine when a finding may be biologically plausible. Therefore evidence from various epidemiological studies is needed to address the methodological issues raised in this thesis.

In the following perspective I would like to call special attention to some of the more important issues: 1) sample size considerations; 2) spontaneous abortions and prenatal diagnosis; 3) unmeasured confounding, 4) long-term follow-up of morbidity in the offspring; and 5) a system for monitoring the teratogenic potential of new drugs.

Sample size

Birth defects can't be considered as a single homogenous outcome, since defects vary according to their embryologic tissue of origin, their gestational occurrence and mechanism of development.[5] The fact that a teratogenic drug increases only the rates of selected defects, has a dramatic effect on the sample size requirements, since specific defects occur with a much lower prevalence than overall birth defects (figure 7.1). This was clearly demonstrated in our studies of loratadine and risk of hypospadias presented in chapter 3 and 4. We learned that loratadine is a common drug, but infrequently used during pregnancy. The infrequent use combined with low prevalence of hypospadias produced only one exposed case in a population of around 95,000 pregnancies. Possible solutions to this lack of precision are nationwide studies (like the one described in chapter 5) or preferably, even larger studies based on international collaboration. Recently, we have started two Nordic studies in collaboration with research groups from Sweden and Finland, with the aim of examining the safety of selected drugs used during pregnancy in large population-based cohorts.

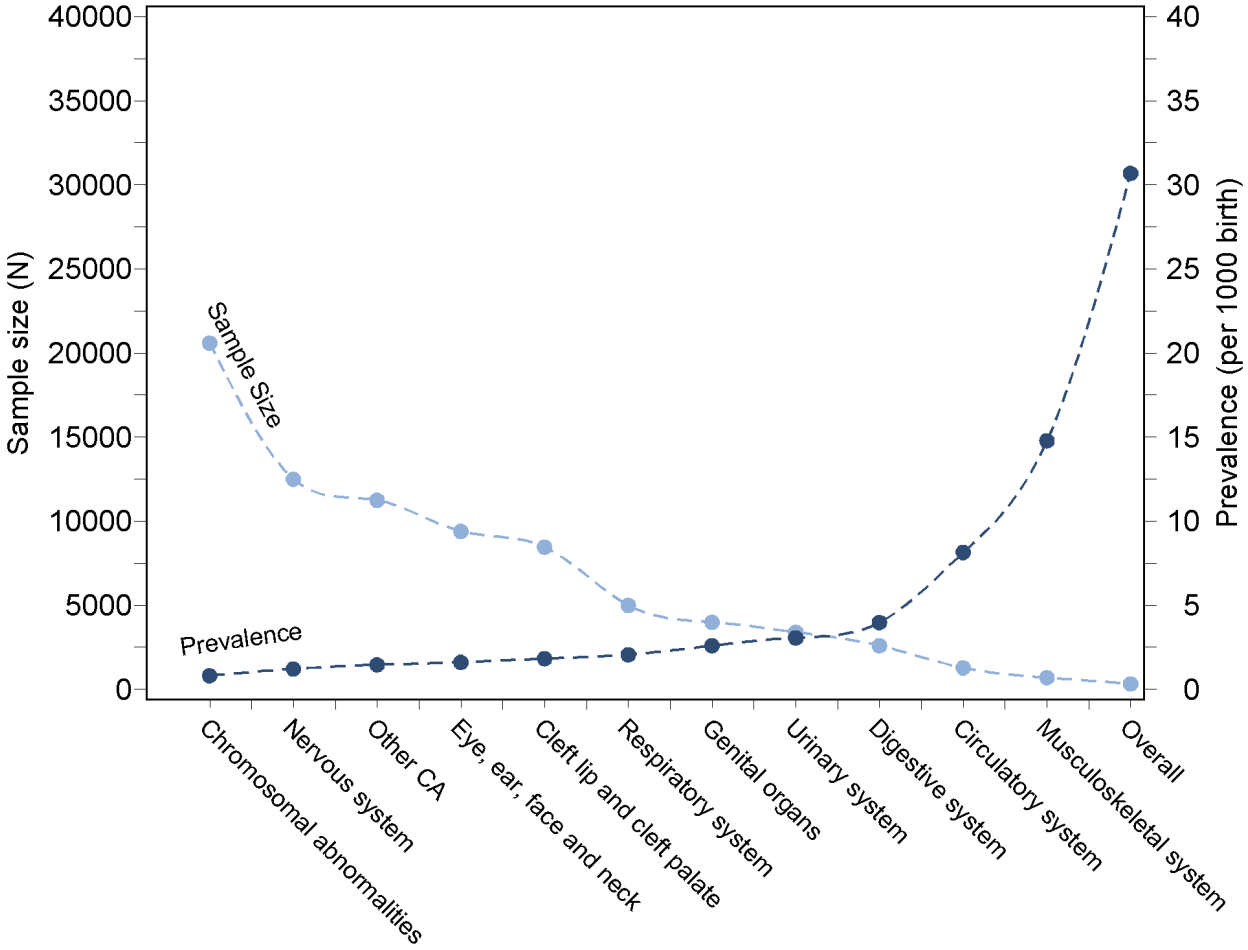

Figure 7.1 The number of exposed pregnancies needed to detect a relative risk of 2.0. Prevalence estimates from the Danish National Registry of Patients based on around 60,000 pregnancies in the Danish Medical Birth Registry in 2007 (alpha=0.05, power=80%, prevalence of exposure=20%).

Spontaneous abortions and prenatal diagnosis

Most studies have focused on the prevalence of birth defects measured at birth, and few studies have addressed spontaneous abortions as an outcome and consequently effects of drugs always leading to abortion will never be detected in these studies. In addition, a growing proportion of birth defects are detected prenatally, sometimes leading to pregnancy termination, which will cause bias if abortion is caused by drug exposure (or underlying disease). In the Danish registries, however, it is possible to study effects of drugs taken during pregnancy in relation to spontaneous abortions. This was demonstrated in chapter 3 and it should be recommended to use this design more frequently in future studies of the safety of drugs used during pregnancy. From 2006 on, a therapeutic induced abortion performed after a malformation is detected by prenatal diagnosis in week 12 or later, is recorded in the DNRP and coded according to the ICD-10 classification.[6] Denmark is unique even among the Nordic countries in offering the possibility of studying birth defects detected at prenatal diagnosis. Inclusion of these outcomes in studies of teratogenic effects of medications will reduce selection bias.

In an ideal prospective study women should be enrolled before conception and the occurrence of events trough out gestation should carefully be monitored. The Internet is a promising modern tool for recruiting women planning to become pregnant. Accurate data on drug use before and during pregnancy obtained from Internet-based questionnaires can be linked to prescription databases and outcome registries in Denmark. We have recently received a grant from the US National Institutes of Health to develop such an Internet-based enrolment tool.[7]

Unmeasured confounding

An important challenge for future studies is the development of a better understanding of risk factors for birth defects. The few known risk factors include, for instance, geography, maternal age, race, and socioeconomic status, whereas the effects of ethnic background and alcohol consumption need further study. In the four studies included in this thesis, we had limited data on potential confounding factors, like maternal and paternal age, smoking, maternal diseases, BMI and use of other drugs. However, data on other potential risk factors – geography, race, and socioeconomic status – are available from other Danish population registries. It would be a major step forward if reliable data on alcohol consumption or the use of over-the-counter medications could be recorded in the DMBR, as it is in the Swedish Birth Registry.[8] In chapter 4 it was shown that such self-reported data can be obtained and linked to outcome registries.

The indication for prescribing the drug is probably one of the most important confounding factors in epidemiological studies of drug-induced birth defects. All available study designs can to some extend control for this in the analysis stage, but it requires that valid and complete information is obtained and translated into standardized and measurable criteria for the 'reason' of prescribing the drug. In practice it is difficult to adjust properly for the reason of prescribing the drug and to differentiate the drug effect from that of the underlying medical condition. However, these methodological problems can with some success be solved if we consider cases as their own control, as is done under the case-crossover design. In this design the use of drugs is assumed to be independent of the duration of pregnancy and the specific birth defect is assumed to be an acute adverse event produced by a transient drug effect.[5] However, if the drug use changes over the time period of study sampling, controls are needed to separate the time trend effect from that of drug use.[9] This modification of the case-crossover design is called the case-time-time-control design. It should be emphasized, that if the birth defect under study is believed to be caused by fluctuation in the underlying disease, rather than the treatment, confounding by indication is still an issue in this design.[4] Despite this, the case-crossover design eliminates confounding by time-stable factors and

is considered to be a very promising new development in pharmacovigilance and future studies of drug-induced birth defects.[4]

Long-term follow-up of morbidity in the offspring

As demonstrated in this thesis, there exists a unique possibility to link Danish registries and databases, including the DMBR, the DNRP and the nationwide prescription database. This comprehensive system of linkable data allows for large studies of low cost, with the unique possibility to prospectively monitor the morbidity in children exposed in utero. Not more than 40 years ago it was inconceivable to some experts, that drugs could produce serious events in adult offspring of exposed mothers. However, it was shown, for instance, that maternal exposure of diethylstilbestrol can produce vaginal cancer in offspring of exposed mothers, which emphasize the need and potential for studies on Danish data sources with long and complete follow-up, spanning generations.[10,11]

A system for monitoring the teratogenic potential of new drugs

Many new drugs have been released on the market in the recent years and gradually some of them will be also used during pregnancy. Despite this, the outcomes after prenatal exposure to these drugs are not reported or monitored in any systematic way in most countries.[4] For this reason, we suggest to set up a running monitoring, based on secondary data sources, of short- and long-term consequences for offspring exposed in utero to newly marketed medications. Ideally one would want to set up a system sensitive enough to pick up all birth defects. To avoid too many false positive signals, the findings should then be scrutinized using a system design with high specificity. Data from several data sources worldwide are likely required in order to achieve a system with both a high sensitivity and specificity.[4] Recently, we have been involved in a European project (www.ALERT-project.org), with the aim of setting up a population based monitoring system for studies of adverse drug reactions.

Monitoring of "over the counter" drugs and drugs with a low rate of compliance would ideally require obtaining self-report and would therefore be more expensive to do. Despite this, primary collected data could easily, at least in the Nordic countries, be linked into such a system and would be a major step forward for monitoring the safety of drugs taken during pregnancy.

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CHAPTER 8

Summary

After thalidomide, initially believed to be safe for use during pregnancy, was shown to cause phocomelia, another extreme common belief became that every drug potentially was a new thalidomide. However, only 30-40 drugs to date are known human teratogens.[1,2] A recent example of a medicinal agent being under suspicion for teratogenicity is the reported association between the anti-allergic drug loratadine and risk of hypospadias, which is one of the topics in this thesis.[3]

Randomized trials of medicines are not conducted among pregnant women for ethical reasons.[4] Therefore observational studies need to supplement animal models in creating the optimal background for the clinical decision making regarding drug use in pregnancy. Most pharmacoepidemiological studies consider specific birth defects, which are rare, and therefore require very large sample size both for reliable estimation of risks (reducing type I error rate) and providing assurance of the safety (reducing type II error rate).[5]

All pharmacies in Denmark use databases in connection with the accounting of the prescription by the National Board of Health. We have linked those prescription databases to the Danish Birth Registry to regional hospital registries and to the National Registry of Patients, aiming to develop a nationwide cohort for studying safety of drugs use in pregnancy.[6-15] Use of such existing routinely maintained databases in medical research has many advantages, the main one being readily available collected data, implying that a study with a large number of subjects can be done in a fraction of time and cost that would be required for an equivalent study with primary data collection.[16]

Limitations of registry-based data, which are often ignored,[16] are related to data quality since the methods of data collection are predetermined by administrative needs, and are sometimes impossible to validate.

Therefore the aims of this thesis were:

- To provide an overview of methodological problems related to using health care databases for studying safety of drug use in pregnancy (chapter 2).
- To study the safety of use of a drug commonly used in pregnancy, such as non-steroidal inflammatory drugs (chapter 3).

- To study the association between the birth defect hypospadias and maternal use of a commonly used anti-allergic drug, loratadine (chapters 4, 5 & 6).

Population-based registries in the Nordic and other countries enable individual-level record linkage of prospectively and retrospectively collected information from databases tracking maternal prescriptions, births, and birth defects. These databases have accumulated millions of person-years of follow-up, thereby reducing random error around estimates of effect in studies that use their data. Systematic error (bias), by contrast, cannot be remedied by increasing the number of observations, and large non-randomized studies remain subject to selection bias, information bias, and confounding.

In studying teratogenicity of medications, there are two major sources of selection bias: spontaneous fetal loss (extra-uterine pregnancy, spontaneous abortion, stillbirth) and induced abortion. If only birth defects observed at birth are documented, such selection bias can result in a spurious apparent association between drug exposure and medicinal agent or, alternatively, lead to erroneous conclusion of the lack of an association.[17] In order to reduce selection bias, it is important to include data on birth defects observed not only at birth (live or still) but, if possible, at spontaneous abortion and during prenatal diagnosis.[18] For example, in Denmark, it is possible to identify from the DNRP women experiencing a spontaneous abortion or undergoing an induced abortion.

Information bias arises from coding, diagnostic, or classification errors. Misclassification of drug use in register-based studies is likely to be non-differential, since exposure data are collected independently of and prior to diagnosing birth defects. While coding errors are inevitable in the records of hospital diagnosis, the specificity of birth defects diagnoses in the computerized databases is likely to be high (false-positive rate low); given perfect specificity, imperfect sensitivity alone is not expected to bias relative estimates. Confounding by indication is of special concern in studies of unintended effects of medications. Systematic errors due to misclassification and confounding are difficult to avoid in data routinely collected for non-research purposes. It is therefore desirable to conduct sensitivity analyses in order to quantify potential impact of misclassification or confounding on study findings.

In chapter 3 we report results of a population-based study in the Danish county of North Jutland (population approximately 490,000) to estimate the risk of birth defects and other adverse outcomes after prenatal exposure to non-steroidal anti-inflammatory drugs. We found no increased risk of preterm birth, low birth weight or birth defects among 1,462 pregnant women who had taken up prescriptions for NSAIDs in the period from 30 days before conception until end of pregnancy. However, in a case-control

study with 4268 cases, we found that use of non-steroidal anti-inflammatory drugs was associated with an increased risk of spontaneous abortion (these findings have recently been replicated in a updated Danish dataset based on 19,690 cases, see appendix I). We could not determine whether this association was causal, since we could not rule out alternative explanations, such as confounding by indication.

In chapter 4, we examined the self-reported use of anti-allergic drugs in pregnancy and the risk of hypospadias. We conducted a nested case-control study, based on women enrolled in the Danish National Birth Cohort from 1998 to 2002. Information on maternal use of anti-allergic drugs in pregnancy was retrieved from telephone interviews and questionnaires completed by all women enrolled in the birth cohort. These data did not indicate an increased risk of hypospadias associated with the use of either loratadine or other antihistamines, but the precision of study estimates was low, indicating the need for even larger studies in order to rule out an association definitively. Compared with studies relying on prescription databases to ascertain drug use, the study's strengths were: i) ascertainment the actual drug intake by the pregnant woman; and ii) inclusion of information on non-prescription drugs. Despite this, the exposure rate of loratadine among controls was not greater than the exposure rate found in a parallel nationwide study based on prescription databases (described below). In fact, the exposure rate for other antihistamines based on nationwide prescription data was 2.7% compared with a rate of 2.4% in this study, based on self-reported data. The agreement between the two data sources is reassuring.

In chapters 5 and 6, we presented two studies investigating the risk of hypospadias among offspring of mothers who used loratadine and other anti-allergic drugs during pregnancy. The first study was conducted in four Danish counties, which account for 30% of the Danish population (~1.6 million) and was based on regional prescription databases. The second study, a nationwide extension of the first study, was based on a nationwide prescription database hosted by Statistic Denmark. Neither of the studies showed a significantly increased risk of hypospadias among women with prescriptions for loratadine in the first trimester and up to 30 days before conception. In fact, among the 1575 cases of hypospadias, the adjusted odds ratio among users of loratadine relative to non-users was 0.6 (95% CI: 0.3-1.4) and the corresponding odds ratio for other antihistamines was 1.3 (95% CI: 0.9-1.9).

Chapter 7 covers the conclusion and the perspectives for future registry-based research within drug-induced birth defects.

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CHAPTER 9

Resumé

Af etiske årsager gennemføres der ikke randomiserede studier af lægemidlers sikkerhed under graviditeten på grund af risikoen for medfødte misdannelser. Derfor er observationelle studier baseret på registre et vigtigt instrument til at skabe viden og danne grundlag for kliniske retningslinjer i forbindelse med brug af lægemidler under graviditeten. Der kendes til dato omkring 30-40 lægemidler med teratogene effekter, hvor thalidomid er det mest kendte lægemiddel. NSAID-præparater, som er den hyppigste anvendte gigtmedicin i befolkningen, anvendes i stort omfang af gravide på trods af at sikkerheden ikke er fastslået. Det samme gælder det hyppigt anvendte lægemiddel mod allergi, loratadin, som har været mistænkt for at fremkalde en misdannelse i urinvejene, hypospadi.
Formålet med den aktuelle ph.d.-afhandling har været at undersøge sikkerheden for ovennævnte lægemidler hos danske gravide. Afhandlingen er baseret på danske registre ligesom der er foretaget en gennemgang af metodeproblemer ved studier af lægemidlers sikkerhed under graviditeten.

Alle recepter som indløses på apoteker i Danmark registreres i dag elektronisk. Med henblik på at studere en række lægemidlers sikkerhed under graviditeten har Klinisk Epidemiologisk afdeling opbygget en forskningsdatabase ved at sammenkøre recept-oplysninger fra den offentlige sygesikring med oplysninger fra Det Medicinske Fødselsregister, hospitalernes administrative informationssystemer og Landspatientregisteret. Der er flere fordele ved at benytte disse rutine-indsamlede data i den epidemiologiske forskning. F.eks. er registreringen af lægemidler i receptdatabasen (eksponeringen) og registreringen af fødselsudfald uafhængige, undersøgelserne kan baseres på store studiepopulationer samt udføres relativt hurtigt og billigt. Både fordele og ulemper ved brug af disse registre diskuteres indgående i afhandlingen.

Baseret på disse datakilder, undersøgte vi risikoen for lav fødselsvægt, for tidlig fødsel og misdannelser hos børn til gravide kvinder, der havde indløst en recept på NSAIDs i perioden 30 dage før befrugtning og op til udgangen af 1. trimester. Vi fandt ingen forøget risiko sammenlignet med gravide kvinder der ikke havde indløst en recept på NSAIDs i tilsvarende periode. Dog fandt vi en betydelig sammenhæng mellem indløsning af recept på NSAIDs og risikoen for spontan abort.

I den danske nationale fødselskohorte, Bedre Sundhed for Mor og Barn, undersøgte vi sammenhængen mellem brug af loratadin og andre lægemidler mod allergi og risikoen for hypospadi. I undersøgelsen,

som var baseret på selvrapporterede oplysninger om lægemiddel-forbrug i graviditeten, fandt vi ingen sammenhæng med hypospadi. Vi undersøgte ligeledes hypotesen i henholdsvis et regionalt og landsdækkende studie baseret på lægemiddel-oplysninger fra receptdatabaser. I ingen af de to studier fandt vi en sammenhæng mellem loratadin og andre antihistaminer og risikoen for hypospadi.

APPENDIX I

Risk of birth defects and spontaneous abortion among users of non-steroidal anti-inflammatory drugs in the period 1999-2008: Methodological issues

In chapter 2 several methodological issues have been described in relation to studies of drug induced birth defects. To exemplify this, we will examine the risk of birth defects and spontaneous abortion among women exposed to NSAIDs in pregnancy, based on several analytic strategies. The analyses are based on data from Danish data sources. We have linked population based registries and prescription databases in four Danish counties, which account for 30% of the Danish population, and identified pregnancies in the period between 1999 and 2008. A detailed description of these data sources can be found in chapter 3 and 5.

Case-control design

We identified n=6,232 birth defects from the Danish National Registry of patients and selected 10 births per case (matched on year of birth) from the Danish Medical Birth Registry. In total, n=72,864 cases and controls were identified with a full maternal prescription history in the period from 1999-2008. The first trimester and up to 30 days before conception was considered as the critical period. The distribution of non-steroidal anti-inflammatory drugs (NSAIDs) in this period for cases and controls is shown in table A.1.

Table A.1 A case-control design showing the risk of birth defects among women exposed to NSAIDs in the first trimester and up to 30 days before conception.

Exposure to NSAIDS	**Controls (n=66,240)**	**Cases (n=6,624)**	**OR* (95% CI)**
	N (%)	**N (%)**	
Non exposed	64,424 (97.3)	6,428 (97.0)	Reference
Exposed	1,816 (2.7)	196 (3.0)	1.0 (0.9-1.2)

*adjusted for maternal age, gestational age, parity, smoking and diabetes

We conducted similar analyses according to specific birth defects. The results are presented in table A.2.

Table A.2. The risk of specific birth defects among women exposed to NSAIDs in the first trimester and up to 30 days before conception.

Type	**Exposed / N (%)**	**OR* (95% CI)**
Controls	1,816 / 64,424 (2.7)	Reference
Nervous system	8 / 221 (3.6)	1.3 (0.6-2.8)
Eye, ear, face and neck	8 / 266 (3.0)	0.9 (0.4-1.9)
Circulatory system	45 / 1561 (2.9)	0.9 (0.6-1.2)
Respiratory system	4 / 263 (1.5)	0.6 (0.2-1.7)
Cleft lip and cleft palate	12 / 296 (4.1)	1.6 (0.8-3.0)
Digestive system	16 / 526 (3.0)	1.1 (0.7-1.9)
Genital organs	17 / 620 (2.7)	0.8 (0.5-1.4)
Urinary system	9 / 416 (2.2)	0.8 (0.4-1.7)
Musculoskeletal system	83 / 2676 (3.1)	1.2 (1.0-1.5)
Other CA	22 / 610 (3.6)	1.2 (0.7-1.9)
Chromosomal abnormalities	3 / 184 (1.6)	0.6 (0.2-2.1)

*adjusted for maternal age, gestational age, parity, smoking and diabetes

Prenatal diagnosis

Pregnancies terminated due to prenatal diagnosis may bias the relative risk estimates. To explore this further, we identified n=117 birth defects in the National Registry of Patients, detected and terminated following prenatal diagnosis. Again, we selected 10 live births per case (matched on year of birth) from the Danish Medical Birth Registry. In total, n=2,333 cases and controls were identified with a full

maternal prescription history. However, only one case (0.9%) was exposed to NSAIDs in the critical period, compared to 2.4% among controls.

Spontaneous abortions

From the National Registry of Patients we identified n=19,690 spontaneous abortions in the period between 1999 and 2008. We selected three live births per case (matched on year of birth and time since conception) from the Danish Medical Birth Registry. In total, n=78,241 cases and controls were identified with a full maternal prescription history. The risk estimates were calculated for time intervals of 0-1, 0-2, 0-4, 0-6 and 0-12 weeks prior to the index date (date of admission for cases and corresponding gestational week for live birth controls). We had no information about smoking and parity. Other potential confounding factors like maternal age, diabetes and co-medication did not affect the risk estimates. The crude estimates are presented in table A.3.

Table A.3 The risk of spontaneous abortion according to the timing of NSAID use prior to index date.

Time interval prior to index date	**Cases (n=19,690) Exposed (%)**	**Controls (n=58,551) Exposed (%)**	**OR (95% CI)**
0-12 weeks	637 (3.2)	1449 (2.5)	1.3 (1.2-1.5)
0-6 weeks	256 (1.3)	503 (0.9)	1.5 (1.3-1.8)
0-4 weeks	166 (0.8)	285 (0.5)	1.8 (1.5-2.1)
0-2 weeks	88 (0.6)	97 (0.2)	2.7 (2.0-3.7)
0-1 weeks	54 (0.3)	41 (0.1)	4.0 (2.6-5.9)

Sensitivity analyses

We found a four-fold increased risk of spontaneous abortions among women exposed to NSAIDs within 0-1 week prior to index date relative to non-exposed women in the same interval. To validate the strength of this association the following sensitivity analyses are applied, mainly in relation to misclassification of NSAID exposure.

1. In week 0-1 the exposure prevalence among cases and controls was 0.3% and 0.1%, respectively. If we assume that that 20% of exposed cases do not take the medication (and therefore classify them as non-exposed), the odds ratio will be reduced from 4.0 (2.6-5.9) to 3.2 (2.0-4.8). Thus, compliance does not seem to have a dramatic effect on the risk estimates.
2. In week 0-1 the exposure prevalence among controls was 0.1%. We assume that additional 0.1% of cases and controls are exposed to NSAIDs over-the-counter. Thus, if we consider them as exposed, the odds ratio will be reduced from 4.0 (2.6-5.9) to 2.2 (1.6-3.0).
3. Since the exposure prevalence decreases after conception, it is important to compare cases and controls in the same 'window' of gestation. Therefore the validity of the coding of the admission date and gestational age is important. If for instance the week of gestation among controls, by mistake, are shifted one week 'to the left', cases in week 6, say, are incorrectly compared with controls in week 7. To address this bias, we have shifted the index date among controls one week 'to the left' and one week 'to the right', respectively. The odds ratio of spontaneous abortion among women exposed to NSAIDs 0-1 week prior to index date relative to non-exposed in the same interval, was under this assumption 2.8 (2.0-4.1) and 4.3 (2.9-6.6), respectively.

Case-Time-Control design

To address the problem of confounding by indication in relation to NSAIDs and spontaneous abortions, we evaluated the association in a case-cross-over and case-time-control design. Use of NSAIDs 0-1 week before the date of admission was considered to be the critical period compared to a similar one week period 12 weeks earlier. The case-cross-over OR 0-1 week before index date was 0.7 (0.5-1.0). However in the corresponding case-time-control design, where the time trend effect was eliminated, the case-time-control OR was 3.6 (2.2-5.8). In comparison, as shown in table A.3, the case-control OR 0-1 week before index date was 4.0 (2.6-5.9). Thus, if the four-fold increased risk was due to confounding by indication, the case-time-control design was not able to eliminate this factor.

APPENDIX II

Publications originating from this thesis

The publications originating from this thesis are attached in the following order:

Risk of adverse birth outcome and miscarriage in pregnant users of non-steroidal anti-inflammatory drugs: population based observational study and case-control study

Gunnar Lauge Nielsen, Henrik Toft Sørensen, Helle Larsen, Lars Pedersen

BMJ 2001;322:266-70

Prenatal exposure to loratadine in children with hypospadias: A nested case-control study within the Danish National Birth Cohort

Lars Pedersen, Mette Nørgaard, Mette Vinther Skriver, Jørn Olsen, Henrik Toft Sørensen

Am J Ther. 2006;13:320-4

Maternal use of loratadine during pregnancy and risk of hypospadias in offspring

Lars Pedersen, Mette Vinther Skriver, Mette Nørgaard , Henrik Toft Sørensen

Int J Med Sci 2006;3:21-25

Maternal use of loratadine during pregnancy and prevalence of hypospadias in offspring: A Danish nationwide case-control study

Lars Pedersen, Mette Nørgaard, Kenneth J. Rothman, Henrik Toft Sørensen

Epidemiology 2008;19:359-60.

Risk of adverse birth outcome and miscarriage in pregnant users of non-steroidal anti-inflammatory drugs: population based observational study and case-control study

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Abstract

Objective To estimate the risk of adverse birth outcome in women who take non-steroidal anti-inflammatory drugs during pregnancy.
Design and setting Population based cohort study and a case-control study, both based on data from a prescription registry, the Danish birth registry, and one county's hospital discharge registry.
Participants Cohort study: 1462 pregnant women who had taken up prescriptions for non-steroidal anti-inflammatory drugs in the period from 30 days before conception to birth and 17 259 pregnant women who were not prescribed any drugs during pregnancy. Case-control study: 4268 women who had miscarriages, of whom 63 had taken non-steroidal anti-inflammatory drugs, and 29 750 primiparous controls who had live births.
Main outcome measures Incidences of congenital abnormality, low birth weight, preterm birth, and miscarriage.
Results Odds ratios for congenital abnormality, low birth weight, and preterm birth among women who took up prescriptions for non-steroidal anti-inflammatory drugs were 1.27 (95% confidence interval 0.93 to 1.75), 0.79 (0.45 to 1.38), and 1.05 (0.80 to 1.39) respectively. Odds ratios for the taking up of prescriptions in the weeks before miscarriage ranged from 6.99 (2.75 to 17.74) when prescriptions were taken up during the last week before the miscarriage to 2.69 (1.81 to 4.00) when taken up between 7 and 9 weeks before. The risk estimates were no different when the analysis was restricted to missed abortions.
Conclusions Use of non-steroidal anti-inflammatory drugs during pregnancy does not seem to increase the risk of adverse birth outcome but is associated with increased risk of miscarriage.

Introduction

Anti-inflammatory drugs are among the commonest drugs prescribed to pregnant women.[1 2] All non-steroidal anti-inflammatory drugs are inhibitors of cyclo-oxygenase and can have adverse effects in both mother and fetus.[3] Some investigators have linked fetal exposure to aspirin or indomethacin with a higher risk of congenital abnormality and low birth weight,[4 5] though other investigators have failed to confirm this.[6–9] The risk of adverse birth outcome in users of non-steroidal anti-inflammatory drugs other than aspirin and indomethacin has been examined only in studies with low numbers of participants, and few have been population based.[10]

As non-steroidal anti-inflammatory drugs are widely used, even a small increase in the risk of adverse effects may have major implications for public health. We examined the risk of adverse birth outcome among Danish women who had taken up prescriptions for non-steroidal anti-inflammatory drugs during pregnancy.

Subjects and methods

Study population

The study was conducted in the Danish county of North Jutland (population approximately 490 000). It included data on all women who between 1991 and 1998 had a live birth or a stillbirth after the 28th week of gestation or who had a miscarriage (including missed abortions). The data were obtained from the Danish birth registry and the county's hospital discharge registry. Risk of adverse birth outcome (congenital abnormality, low birth weight, and preterm birth) was examined in a cohort study and risk of miscarriage in a case-control study.

Use of non-steroidal anti-inflammatory drugs

As part of its tax funded health care for all inhabitants the Danish national health service reimburses 50% of all expenditure on a wide range of prescribed medicines, including non-steroidal anti-inflammatory drugs (international anatomical therapeutical classification code M01A) prescribed at doses equivalent to 400 mg or 600 mg ibuprofen (doses equivalent to 200 mg ibuprofen may be purchased without a prescription). North Jutland is served by 33 pharmacies equipped with electronic accounting systems that are used primarily to secure reimbursement from the national health service. These systems include information on the anatomical therapeutical classification code, the amount of the drug prescribed, the personal identification number of the patient, and the date of dispensing the drug.[11] All data are transferred to the pharmaco-epidemiological prescription database of North Jutland, which holds key data on all reimbursed prescribed drugs sold at pharmacies in the county since 1 January 1991.[12] During the period studied indomethacin was regarded as the drug of choice to delay premature delivery. As this may introduce a confounding factor, our analyses both included and excluded data on women who took indomethacin during pregnancy. We validated data on the use of non-steroidal anti-inflammatory drugs by verifying prescriptions in general practitioners' and hospital records of a randomly selected subset of 46 pregnant women.

Outcome data

Registries

The Danish birth registry, which comprises data collected by midwives and doctors attending deliveries, contains information on all births in Denmark since 1

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Further data on congenital abnormalities appear on the BMJ's website

January 1973.[13] The main data are maternal age, self reported smoking status, order of birth, gestational age, length and weight of neonate at birth, and personal identifiers for both mother and child.

We identified all cases of congenital abnormality and miscarriage from the regional hospital discharge registry (established in 1977), from which data are transferred to the national Danish hospital discharge registry. The national registry comprises data on 99.4% of all discharges from Danish hospitals and includes 10 digit personal identifiers, dates of admission and discharge, the surgical procedures performed, and up to 20 diagnoses,[14] classified according to the Danish versions of ICD-8 (international classification of diseases, 8th revision) until the end of 1993 and ICD-10 after this date. The codes for miscarriage were 634.61, 643.8-9, and 645.1 in ICD-8 and O02 and O03 in ICD-10, and those for congenital abnormalities were 740.00-752.09, 752.29-755.59, and 755.79-759.99 in ICD-8 and Q00.0-Q52.9, Q54.0-Q64.9, and Q66.0-Q99.9 in ICD-10. Diagnoses of congenital dislocation of the hip and undescended testis were excluded because of their low validity.

The personal identifiers were used to link prescription records with both registries. Follow up, using the regional hospital discharge registry, ended on 31 December 1998.

Cohort analysis

The association between use of non-steroidal anti-inflammatory drugs and adverse birth outcome was studied in a cohort of women who had a live birth or a stillbirth after the 28th week of gestation. The women were divided into two groups according to the stage of gestation (based on information from the birth registry) at which they took up prescriptions for non-steroidal anti-inflammatory drugs: the "early pregnancy" group comprised women who took up prescriptions from 30 days before conception to the end of the first trimester and the "later pregnancy" group comprised women who took up prescriptions in the second or third trimesters. The reference group was all pregnant women who were not prescribed any kind of reimbursed medicine in the study period. To determine whether there was a dose-response relation, we compared the outcomes of pregnancies of women during which only one prescription of a non-steroidal anti-inflammatory drug was recorded with those of women in which more than one prescription was recorded.

Case-control analysis

We used a case-control study to determine any association between non-steroidal anti-inflammatory drugs and first recorded miscarriage. Cases were defined as first recorded miscarriages in women who had taken up a prescription for non-steroidal anti-inflammatory drugs in the 12 weeks before the date of discharge from hospital after the miscarriage. The control group was primiparous women who had live births. The first trimester was used as the exposure period in the control group. The risk estimates were calculated for time intervals of 1, 2-3, 4-6, 7-9, and 10-12 weeks before the day of discharge after miscarriage. All non-steroidal anti-inflammatory drug prescriptions were categorised according to these periods.

Statistical analysis

Cohort study

We performed logistic regression analyses to estimate the risk of congenital abnormality, low birth weight (<2500 g), and preterm birth (<37 weeks) associated with non-steroidal anti-inflammatory drugs, adjusted for maternal age, birth order, and smoking status. We used data from the early pregnancy group to estimate the risk of congenital abnormality and data from the later pregnancy group to estimate the risk of preterm birth and low birth weight (analysis of risk of low birth weight was restricted to full term births).

Case-control study

We performed logistic regression analyses to estimate the risk of miscarriage associated with non-steroidal anti-inflammatory drugs. We included as a variable the period of time from when the prescription was taken up to the day of discharge after the miscarriage, adjusting for maternal age.

Table 1 Comparison of pregnancies during which prescriptions for non-steroidal anti-inflammatory drugs were taken up and those during which no drugs were prescribed.

	Prescriptions taken up			
Variable	Between 30 days before conception and end of first trimester	In second and third trimester	Any time from 30 days before conception to term	No drug prescribed during pregnancy
No of pregnancies	1106	997	1462	17 259
First pregnancies	449	381	576	9 263
Subsequent pregnancies	657	616	886	7 996
No of prescriptions	1257	1176	1742	—
Mean age (range) of mothers	28.1 (16-43)	28.3 (16-43)	28.3 (16-43)	28.5 (13-47)
No (%) of smokers	398 (36)	409 (41)	600 (41)	4 833 (28)
Gestational age:				
≥37 weeks	1041	936	1374	16 268
34-6 weeks	41	40	59	682
<34 weeks	24	21	29	309
Mean weight (range) of babies at birth (grams)	3464 (639-5530)	3453 (639-5710)	3466 (639-5710)	3 483 (605-5 630)
No (%) of babies with congenital abnormalities	46 (4.2)	37 (3.7)	56 (3.8)	564 (3.3)
No (%) of preterm deliveries	65 (5.9)	61 (6.1)	88 (6.0)	991 (5.7)
No (%) of babies of low birth weight at term*	19 (1.8)	13 (1.4)	22 (1.6)	268 (1.6)

*Excluding preterm deliveries.

Table 2 Logistic regression analyses of birth outcome in women who took up prescriptions for non-steroidal anti-inflammatory drugs during pregnancy and in women who were not prescribed any drug during pregnancy. Figures are crude and adjusted odds ratios (95% confidence intervals)

	Congenital abnormalities		Low birth weight		Preterm delivery	
Variable	**Crude**	**Adjusted**	**Crude**	**Adjusted**	**Crude**	**Adjusted**
Drugs:						
No drugs prescribed	1	1	1	1	1	1
Prescriptions taken up	1.29 (0.95 to 1.75)	1.27 (0.93 to 1.75)	0.84 (0.48 to 1.47)	0.79 (0.45 to 1.38)	1.07 (0.82 to 1.40)	1.05 (0.80 to 1.39)
Pregnancy:						
First	1	1	1	1	1	1
Subsequent	0.86 (0.73 to 1.01)	0.84 (0.70 to 1.01)	0.63 (0.50 to 0.81)	0.59 (0.45 to 0.77)	0.79 (0.69 to 0.89)	0.74 (0.64 to 0.85)
Smoking status:						
Non-smoker	1	1	1	1	1	1
Smoker	1.16 (0.97 to 1.39)	1.15 (0.96 to 1.38)	3.66 (2.86 to 4.67)	3.72 (2.90 to 4.77)	1.41 (1.23 to 1.61)	1.4 (1.23 to 1.61)
Maternal age:						
<25	1	1	1	1	1	1
25-30	0.89 (0.71 to 1.10)	0.93 (0.75 to 1.16)	0.68 (0.51 to 0.92)	0.93 (0.68 to 1.27)	0.85 (0.72 to 0.99)	0.88 (0.75 to 1.04)
>30	0.93 (0.76 to 1.15)	0.97 (0.76 to 1.23)	0.84 (0.63 to 1.14)	1.28 (0.92 to 1.79)	0.9 (0.77 to 1.07)	1.06 (0.88 to 1.27)

Results

Cohort study

A total of 1462 women who had a live birth or stillbirth after the 28th week took up 1742 prescriptions for non-steroidal anti-inflammatory drugs; 1106 women took up prescriptions in early pregnancy and 997 in later pregnancy (table 1). Apart from a lower proportion of smokers among the women who were not prescribed any drugs, no other significant differences in the study variables were found.

We identified 46 congenital abnormalities in 1106 pregnancies of women who took up prescriptions of non-steroidal anti-inflammatory drugs during early pregnancy (4.2% (95% confidence interval 3.0% to 5.3%)), compared with 564 in 17 259 pregnancies in the reference cohort (3.3% (3.0% to 3.5%)). Details of these congenital abnormalities are shown on the *BMJ*'s website. The adjusted odds ratios of congenital abnormalities, low birth weight, and preterm birth among women who took up prescriptions of non-steroidal anti-inflammatory drugs were 1.27 (0.93 to 1.75), 0.79 (0.45 to 1.38), and 1.05 (0.80 to 1.39), respectively (table 2). There were no stillbirths among the women who took up prescriptions.

Table 3 Prescription of NSAIDs among women recorded as having a miscarriage in their first pregnancy compared with women who had a live birth (reference group). Figures are Nos of pregnancies*

Variable	**Miscarriage (n=4268)**	**Live birth (n=29 750)**	**Adjusted odds ratio (95% CI)**
Time from taking up prescriptions for NSAIDs to date of discharge after miscarriage:			
1-12 weeks	63	318	1
1 week	3	9	6.99 (2.75 to 17.74)
2-3 weeks	5	15	3.00 (1.21 to 7.44)
4-6 weeks	14	41	4.38 (2.66 to 7.20)
7-9 weeks	19	92	2.69 (1.81 to 4.00)
10-12 weeks	22	161	1.26 (0.85 to 1.87)
Maternal age:			
<25 years (reference)	1022	8 284	1
25-29 years	1509	12 424	0.99 (0.91 to 1.07)
30-34 years	1128	6 728	1.36 (1.24 to 1.49)
>35 years	609	2 314	2.13 (1.91 to 2.38)
NSAIDs not prescribed during pregnancy	4205	29 432	

NSAIDs=non-steroidal anti-inflammatory drugs.
*Only primigravidas are included in the analysis.
The comparison period used for the reference group was the first trimester.

Comparison of pregnancies during which more than one non-steroidal anti-inflammatory drug prescription was taken up with those in which only one was taken up gave adjusted odds ratios for taking up more than one prescription of 0.66 (0.20 to 2.17) for congenital abnormalities, 3.09 (0.91 to 10.52) for low birth weight, and 0.65 (0.26 to 1.68) for preterm birth.

Fifty women had taken up prescriptions for indomethacin. Review of hospital records confirmed that the risk of miscarriage was an indication for the prescribing of indomethacin in 38 cases; in 10 use of indomethacin could not be confirmed, and one record could not be traced. Exclusion of these data did not change the risk estimates shown in table 2 (data not shown).

Case-control study

Table 3 shows the odds ratios for miscarriage, compared with pregnancies ending in a birth, in women who took up prescriptions for non-steroidal anti-inflammatory drugs. The ratio decreases as the time from taking up the prescriptions to discharge from hospital increases. Neither restricting the calculations to missed abortions only (ICD-8, 634.61 and 645.1; ICD-10, O02.1) nor inclusion or exclusion of pregnancies during which indomethacin was taken changed the risk estimates given in table 3 (data not shown).

Validation of non-steroidal anti-inflammatory drug use

To validate use of the drugs, we studied a randomly selected subgroup of general practitioners' records and hospital records for 46 pregnancies in the cohort study. In 71% of these pregnancies, the records indicated that non-steroidal anti-inflammatory drugs were prescribed, mostly for benign conditions of the muscles and skeleton.

Discussion

We found no significant association between take up of prescriptions for non-steroidal anti-inflammatory drugs during pregnancy and risk of congenital abnormality, low birth weight, or preterm birth. There was, however, a significant association with miscarriage.

The full and independent registration of prescriptions and birth outcome prevented selection bias and some types of information bias. In the cohort study potential misclassification in the registration of congenital abnormalities would be unlikely to be related to the prescribing of non-steroidal anti-inflammatory drugs. The case-control study was based on routinely recorded data and was independent of diagnosis, thus there was no risk of recall bias, which can invalidate case-control studies that rely on interviews.[15] Previous studies have shown high validity of data in both the prescription database and the birth registry.[16 17] In a recent, as yet unpublished study that was based on a review of hospital records in the period 1 January 1991 to 31 December 1995, we found that more than 80% of patients coded as having a congenital abnormality in the regional hospital discharge registry were correctly coded. Data on the major confounding factors of maternal age, smoking status, and birth order were available in the cohort study; the case-control study, however, lacked data on smoking status.

We had no specific information on compliance. That the prescriptions for non-steroidal anti-inflammatory drugs were taken up at the pharmacy and paid for in part by the patient may improve compliance. Furthermore, a relevant indication for the use of non-steroidal anti-inflammatory drugs was documented in general practitioners' records in a high proportion of pregnancies. These drugs, however, are often used as short term analgesics and may be purchased over the counter, which may increase the likelihood of misclassification of women with respect to drug use and bias the risk estimates towards one.

Teratogens do not uniformly increase the risk of all congenital abnormalities, but rather of specific abnormalities.[15] We did not find any specific trend in the distribution of congenital abnormalities, and we did not find evidence for a dose-response relation between mothers' use of non-steroidal anti-inflammatory drugs and adverse birth outcome. Like other researchers we did not find an increased risk of reduced fetal growth.[8 9]

Use of non-steroidal anti-inflammatory drugs in pregnancy is clearly associated with increased risk of miscarriage. We had no information about the gestational age at time of miscarriage. A critical factor in the case-control study, therefore, is the time period that was selected for the controls, as general practitioners may change their prescribing practice when they know that a woman is pregnant. Such a bias would probably be independent of any particular drug among drugs that have the same estimated risk profile; we therefore repeated the analyses for penicillin V instead of non-steroidal anti-inflammatory drugs and found an odds ratio of 1. This result, as well as the decreasing odds ratio with increasing time interval between time of prescribing of non-steroidal anti-inflammatory drugs and miscarriage, indicates that such bias was minimal but does not exclude the possibility of confounding by indication (for example, the prescribing of a drug to treat pain that may be a precursor of miscarriage). However, we cannot determine from our non-experimental data whether this association is causal or due to undetected confounding. Thus, in the case-control study we were not able to adjust for smoking status, as we did in the cohort study.

What is already known on this topic

Current knowledge on the safety of taking non-steroidal anti-inflammatory drugs during pregnancy is based on studies with small sample sizes

What this study adds

Risk of adverse outcome at birth (congenital abnormality, low birth weight, or preterm birth) was not associated with the taking up of prescriptions for non-steroidal anti-inflammatory drugs during pregnancy

The taking up of such prescriptions was, however, associated with miscarriage

Apart from an unpublished study of use of ibuprofen in a cohort of 3178 pregnant women from the Michigan Medicaid surveillance study,[18] we have not been able to identify any systematic studies of non-steroidal anti-inflammatory drug use in pregnant women. We have not found any studies of the association between non-steroidal anti-inflammatory drugs and miscarriage in humans. Because of the necessarily limited nature of studies of drug safety during pregnancy, it is important that all available data are combined to obtain the highest possible precision in the calculation of risk estimates. Our observation of an increased risk of miscarriage in women exposed to non-steroidal anti-inflammatory drug is new and needs to be confirmed.

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Contributors: GLN helped formulate the primary study hypothesis, discussed core ideas, finalised the study protocol, participated in data collection, analysis, and interpretation of findings, and undertook the main writing of the paper. HTS initiated the formulation of the primary study hypothesis, discussed core ideas, designed the protocol, and participated in data collection, analysis, interpretation of findings, and writing the paper. HL participated in the design of the study, data analysis, and interpretation of findings and edited the paper. LP participated in data collection, conducted the analyses, and took part in interpretation of findings. HTS is the guarantor of the study.

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Impact on malaria morbidity of a programme supplying insecticide treated nets in children aged under 2 years in Tanzania: community cross sectional study

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A table showing the impact of net use on anaemia reported by other trials is available on the BMJ's website. This article is part of the BMJ's trial of open peer review, and documentation relating to this also appears on the website

Abstract

Objective To assess the impact of a social marketing programme for distributing nets treated with insecticide on malarial parasitaemia and anaemia in very young children in an area of high malaria transmission.

Design Community cross sectional study. Annual, cross sectional data were collected at the beginning of the social marketing campaign (1997) and the subsequent two years. Net ownership and other risk and confounding factors were assessed with a questionnaire. Blood samples were taken from the children to assess prevalence of parasitaemia and haemoglobin levels.

Setting 18 villages in the Kilombero and Ulanga districts of southwestern Tanzania.

Participants A random sample of children aged under 2 years.

Main outcome measures The presence of any parasitaemia in the peripheral blood sample and the presence of anaemia (classified as a haemoglobin level of <80 g/l).

Results Ownership of nets increased rapidly (treated or not treated nets: from 58% to 83%; treated nets: from 10% to 61%). The mean haemoglobin level rose from 80 g/l to 89 g/l in the study children in the successive surveys. Overall, the prevalence of anaemia in the study population decreased from 49% to 26% in the two years studied. Treated nets had a protective efficacy of 62% (95% confidence interval 38% to 77%) on the prevalence of parasitaemia and of 63% (27% to 82%) on anaemia.

Conclusions These results show that nets treated with insecticide have a substantial impact on morbidity when distributed in a public health setting.

Introduction

Several studies have shown that malarial parasitaemia is positively correlated with anaemia and that parasitaemia is the primary cause of anaemia in very young children in Africa.[1] As a result, because malarial infection is the norm in high transmission areas, anaemia is common in young children. Assessment of the impact of chemoprophylaxis in Tanzanian infants showed that over 60% of the anaemia could be due to malaria.[2] The emergence and spread of parasite resistance to commonly used antimalarial agents has exacerbated the problem of anaemia in sub-Saharan Africa.[3]

Hopes for controlling malaria and malarial anaemia have recently been revitalised by the demonstration that nets treated with insecticide can reduce morbidity and mortality. A summary of randomised controlled trials showed an average protective effect of about 50% on mild malaria episodes in areas where the rate of transmission of malaria was stable.[4] Moreover, protective effects were shown on the prevalence of parasitaemia with a high level ($>5000/\mu l$) of trophozoites (31%) and on overall mortality (19%). A modest improvement in packed cell volume (a rise of 0.02 (2%)) and weight gain was also observed in children sleeping under treated nets.[4] Large scale implementation of programmes to supply treated nets is under way in several African countries.[5]

It is not known whether the impact of treated nets in the context of well controlled randomised controlled trials can be replicated under programme conditions.[6] We report the first assessment of the impact of treated bed nets when supplied in the context of a large scale social marketing programme (an approach using marketing techniques to promote and distribute socially beneficial interventions rather than commercial products) on morbidity indicators in children aged under 2 years in an area of Tanzania with a high prevalence of malaria.

Methods

Study area and population

Social marketing of treated bed nets started in the Kilombero net project (KINET) in 1997,[7] covering the

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Prenatal Exposure to Loratadine in Children with Hypospadias: A Nested Case-Control Study Within the Danish National Birth Cohort

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The aim of this study was to examine the risk of hypospadias after reported exposure to loratadine and other antihistamines during pregnancy, based on data from the Danish National Birth Cohort. We examined the risk of hypospadias in a nested case-control design based on women enrolled in the Danish National Birth Cohort from 1998 to 2002 (~95,000 pregnant women). Data on maternal use of medicine in pregnancy were retrieved from questionnaires and telephone interviews, and data on birth outcomes were obtained from the Hospital Discharge Registry (HDR). Within the Danish National Birth Cohort, we identified cases with a diagnosis of hypospadias and randomly selected 10 controls per case without such a diagnosis (matched by date of birth). We identified 203 cases of hypospadias recorded in the HDR within 1 year postpartum and 2030 controls. One case (0.5%) and 25 (1.2%) controls reported exposure to loratadine in the first trimester or up to 30 days before the time of conception. The adjusted odds ratio (OR) for hypospadias among users of loratadine relative to nonusers was 0.9 (95% CI: 0.1–6.9) and the corresponding OR for other antihistamines was 0.5 (95% CI: 0.1–1.9). These data do not indicate an increased risk of hypospadias associated with maternal exposure to loratadine. In addition, this study does not suggest any risk differential between maternal exposure to loratadine and other antihistamines. However, the statistical precision of the risk estimates was low.

Keywords: hypospadias, loratadine, pregnancy, drug safety, case-control studies

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INTRODUCTION

Hypospadias is a congenital anomaly characterized by a urethral opening on the ventral side of the penis as a result of abnormal urethral closure at 8 to 14 weeks' gestation.[1] It occurs with a reported prevalence of 0.3% to 0.8% for male livebirths, and since the 1970s, multiple reports have shown an increase in the occurrence of hypospadias.[2–8] There is concern that this increase could result from increasing exposures to endocrine disruptor chemicals in the environment.[1] A variety of risk factors for hypospadias have been studied including endocrine disrupters, gestational and preexisting diabetes, intrauterine growth retardation, in vitro fertilization (IVF), maternal age, and generic factors.[8–18]

Loratadine is a nonsedating antihistamine commonly used for seasonal allergies. It has a half-life

of approximately 10 hours, but an effect on allergic reactions can still be detected at least 2 days after administration.[19]

In 2001, an increased risk of hypospadias associated with maternal use of loratadine was reported from Sweden, with a relative prevalence ratio of 2.39 (95% confidence interval [CI]: 1.43–3.38).[20] Since then, a number of studies have attempted to confirm this association. Both a small study from the Israeli Teratogen Information[21] and a similar small Canadian study showed no increased risk of birth defects among loratadine users.[22] Similarly, in a case-control study conducted by the US Centers for Disease Control and Prevention (CDC), there was no association between use of loratadine during pregnancy and hypospadias. However, this study did not include first-degree hypospadias.[23] Also a recent Danish registry-based case-control study found no association (L. Pedersen, personal communication).

However, the infrequent maternal use of loratadine in the critical period of pregnancy and the prevalence of hypospadias have a major impact on sample size requirements for providing the definitive assurances of the safety of loratadine to the unborn child.[24] There is especially a need for further studies with data on accurate timing on drug intake to explore the association between maternal exposure to loratadine and other aritihistamines and the risk of hypospadias since both hypospadias and use of antiallergy drugs is common, and any causal association may have public health implications. With this background, we conducted a nested case-control study within the Danish National Birth Cohort, which has information on timing, both for use of loratadine and other drugs, as well as on other potential confounders in the critical period of pregnancy.

MATERIALS AND METHODS

We examined the risk of hypospadias in a nested case-control design based on women enrolled in the Danish National Birth Cohort from 1998 to 2002. In 2002, the cohort comprised of approximately 95,000 pregnant women, which represents about 60% of the women invited to participate in the project.[25] Data on maternal use of medicine in pregnancy were retrieved from questionnaires and telephone interviews.[26] Outcome data were obtained from the National Hospital Discharge Registry and linked to the Danish National Birth Cohort by means of the unique national registration number, assigned to each resident of Denmark (CPR number).

Data on use of loratadine and other exposures

At the first pregnancy examination at the GP (usually weeks 6–12 of gestation), before any prenatal test has been conducted, the women were asked to complete a questionnaire regarding use of medicine for the past 3 months. Therefore, in most cases, this questionnaire covered at least periconceptional use of medicine (30 days before conception) and early gestational use in pregnancy. Data on the use of medicine later in pregnancy, not covered by the questionnaire, were collected by using detailed computerized telephone interviews. In total, four interviews were scheduled to take place at around gestational weeks 12 and 30 (interviews 1 and 2) and when the child was 6 and 18 months old (interviews 3 and 4). In all interviews, use of medicine was registered by the brand name and/or the drug code, and time of exposure was assigned in weeks of gestation (ranging from week 12 to week 40). From this registration, we identified users of loratadine, other antihistamines, IVF drugs, antidiabetics, and antiepileptics. Information about smoking, gestational age, and birth order was similarly obtained from these interviews. We obtained information about preeclampsia from the National Danish Hospital Discharge Registry (ICD-10 codes O14 and O15).

Cases of hypospadias and other outcomes

From the National Danish Hospital Discharge Registry, we identified all cases of hypospadias in the National Birth Cohort. A total of 203 cases of hypospadias, recorded within the first year postpartum, were identified between 1998 and 2002. The codes for hypospadias in ICD-10 codes are Q54.0 (hypospadia glandis, n = 51), Q54.1 (hypospadia corporis penis, n = 3), Q54.2 (hypospadia penoscrotalis, n = 5), Q54.3 (hypospadia perinealis, n = 1), Q54.4 (hypospadia penis arcuatos, n = 5), Q54.8 (other specifier hypospadias, n = 2), Q54.9 (hypospadias without any specifications, n = 59), (Children with multiple hypospadias codes, n = 77), Data on other malformations than hypospadias were not used in this study.

Controls

Within the National Birth Cohort, we randomly selected 10 male controls per case matched by date of birth. The controls were selected when their corresponding case was diagnosed with hypospadias.

Statistical analysis

We classified the use of loratadine into 2 groups according to the time of exposure. The first group comprised women exposed from 30 days before conception to the end of the first trimester. The second group comprised, those who were exposed to loratadine at any time during pregnancy. Users of other antihistamines were classified similarly.

We performed conditional logistic regression analyses to estimate the relative prevalence ratio, by virtue of the odds ratio, of hypospadias among users of loratadine compared with nonusers. By including use of other antihistamines, we were able to compare the risk of hypospadias among loratadine users versus other antihistamine users. We adjusted for the following variables in the analysis: maternal age (<25, 25–30, >30) birth order (1, 1+), gestational age (<34 weeks, 34–36 weeks, ≥37 weeks), maternal smoking (yes, no, or no information), reported use of ovulation-inducing drugs (yes, no), reported use of antiepileptics (yes, no), reported use of antidiabetics (yes, no), and preeclampsia (yes, no). Analyses were conducted separately for reported exposure within the first trimester or up to 30 days before conception and for reported exposure during the entire pregnancy or up to 30 days before conception.

All analyses were done using SAS version 8.02 (SAS Institute, Cary, NC).

RESULTS

Approximately 95,000 women were included in the study cohort at the time of this nested case-control study.

Descriptive data for all 203 cases and 2030 controls are shown in Table 1. One case (0.5%) and 25 controls (1.2%) reported exposure to loratadine compared with exposure of 4 cases (2.0%) and 48 (2.4%) controls to other antihistamines.

Table 1. Characteristics of 203 cases of hypospadias (recorded within the first year postpartum) and 2030 control subjects.

Variable	Cases No. (%)	Controls No. (%)
Exposure to loratadine*	1 (0.5)	25 (1.2)
30 days before conception and first trimester	1 (0.5)	12 (0.6)
Second trimester	0 (0.0)	8 (0.4)
Third trimester	0 (0.0)	13 (0.6)
Exposure to other antihistamines*	4 (2.0)	48 (2.4)
30 days before conception and first trimester	2 (1.0)	37 (1.8)
Second trimester	0 (0.0)	10 (0.5)
Third trimester	2 (1.0)	11 (0.5)
Maternal age, y		
<25	19 (9.4)	160 (7.9)
25–30	98 (48.3)	1037 (51.1.6)
>30	86 (42.4)	833 (41.0)
Birth order		
1	115 (56.7)	900 (44.3)
1+	88 (43.3)	1130 (55.7)
Smoking		
Yes	37 (18.2)	345 (17.0)
No	11 (5.4)	141 (7.0)
No information†	155 (76.4)	1544 (76.1)
Gestational age, wk		
≥37	167 (82.3)	1982 (97.6)
34–36	23 (11.3)	41 (2.0)
<34	13 (6.4)	7 (0.3)
Exposure to ovulation-inducing drugs*	2 (1.0)	17 (0.8)
Exposure to antiepileptics*	1 (0.5)	5 (0.6)
Exposure to antidiabetics*	0 (0.0)	4 (0.2)
Preeclampsia	15 (7.4)	45 (2.2)

*Reported exposure during pregnancy or up to 30 days before conception.
†Missing answer or ''not willing'' to answer the question.

In total, 146 of the 203 cases were diagnosed with hypospadias within 6 months postpartum, and none of these had reported exposure to loratadine during the entire pregnancy or up to 30 days before conception.

For exposure within the first trimester or up to 30 days before conception, the adjusted odd ratio of loratadine exposure was 0.9 (95% CI: 0.1–6.4) and the adjusted odds ratio for other antihistamines was 0.5 (95% CI: 0.1–1.9). For exposure within the entire pregnancy or up to 30 days before conception, the adjusted odds ratio of loratadine exposure was 0.4 (95% CI: 0.1–2.8) and adjusted odds ratio for other anti-histamines was 0.7 (95% CI: 0.3–2.1) (Table 2).

DISCUSSION

We found no increased risk of hypospadias associated with the use of either loratadine or any other antihistamine. However, the statistical precision of the risk estimates is low, and, therefore, an association such as the one found in the initial report of the Swedish Birth Registry cannot be refuted entirely.[20]

Our study has strengths and limitations. We have complete and independent registration of birth and birth outcome. Because our case-control study was nested within a birth cohort, the study population was well defined and comparable, which made it possible to select an appropriate control group.

Data on exposure to loratadine and other antihistamines were self-reported, and it is difficult to evaluate the recall accuracy for medications used in pregnancy. Only a few studies have been published, and there are substantial differences among these studies.[27] However, the period between use of loratadine and when it was reported was very short, which may have improved accuracy. Compared with studies based on prescriptions, it is a strength that self-reported data include information about loratadine bought over the counter (without prescription) and that they only include drugs that the women have actually taken (in contrast to merely dispensed as with a prescription database). We thus found the exposure rate among controls in the National Birth Cohort to be slightly higher than the exposure rate found in a recent Danish registry-based study (L. Pedersen, personal communication) (1.2% in our study versus 0.8% for the registry-based study).

The fact that use of loratadine was reported antenatally reduces the risk of differential recall between cases and controls. Findings for example from case-control studies indicate that recall bias in studies of reproductive outcome tends to account for a higher reporting of potentially hazardous exposure after an adverse pregnancy outcome and consequently over-estimates the relative risk.[28]

The validity of the hypospadias diagnosis depends ultimately on the coding in the Danish Hospital Discharge Registry. It is known that discharge diagnoses may be incorrectly coded. However, a previous Danish study from one country found that the birth defect data were of high quality compared with those routinely collected in other countries; about 80%–85% of diagnoses were correctly coded.[29] In addition, the estimated prevalence of hypospadias in our study corresponds with the prevalence reported in other data sets.

The Swedish study,[20] which initially described that maternal use of loratadine was associated with an increased risk of hypospadias, found that the risk was increased 4-fold compared with maternal use of other antiallergy antihistamines. Although our data could not rule out an effect similar to the findings in this study, there were no suggestions of differences between the risk of hypospadias in users of loratadine and the risk in users of other antihistamines.

Our findings agree with the findings of both the recently conducted Danish registry–based study including 227 cases of hypospadias (L. Pedersen, personal communication) as well as the study

Table 2. The association between hypospadias recorded anytime postpartum and maternal use of antihistamines, odds ratios (OR) and 95% confidence intervals (CI).

Variable	Crude OR (95% CI)	Adjusted OR*(95% CI)
Exposure 30 days before conception and first trimester		
Loratadine	0.8 (0.1–6.4)	0.9 (0.1–6.9)
Other antihistamines	0.5 (0.1–2.2)	0.5 (0.1–1.9)
Exposure 30 days before conception and during pregnancy		
Loratadine	0.4 (0.1–3.0)	0.4 (0.1–2.8)
Other antihistamines	0.8 (0.3–2.3)	0.7 (0.3–2.1)

*Adjusted for maternal age, maternal smoking, birth order, gestational age, preeclampsia, and use of ovulation-inducing drugs, anti-epileptics, or antibodies.

reported by the CDC,[23] which included 563 cases of second- or third-degree hypospadias. Similarly, in an Israeli study[21] of 210 pregnancies exposed to loratadine and 265 pregnancies exposed to other antihistamines, there was no increased risk of hypospadias when compared with other antihistamines. The Canadian Multicenter study,[22] which included 161 loratadine-exposed pregnancies but did not include pregnancies exposed to other antihistamines, found no increased risk of hypospadias in the loratadine-exposed group. Thus, the numbers of studies that fail to show an association between maternal loratadine use and hypospadias are increasing, which suggests that the result found in the Swedish study[20] may have been due to chance or bias.

In conclusion, although the precision is low, these data do not indicate an increased risk of hypospadias associated with maternal exposure to loratadine. In addition, this study does not suggest any risk differential between maternal exposure to loratadine and other antihistamines.

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Research paper

Maternal use of Loratadine during pregnancy and risk of hypospadias in offspring

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To examine the risk of hypospadias after exposure to loratadine and other antihistamines during pregnancy, we conducted a population-based case-control study in four Danish counties, which account for 30% of the Danish population (~1.6 M). We obtained data on maternal use of antihistamines from prescription databases, and data on birth outcomes from the Danish Medical Birth Registry (MBR) and the Hospital Discharge Registry (HDR). A total of 65,383 male births with a full prescription history of the mother in the study period from 1989-2002 were available for analysis. Within this cohort, we identified cases with a diagnosis of hypospadias, and 10 selected controls per case without such a diagnosis (matched on birth month, gender and year of birth). We identified 227 cases of hypospadias recorded in the HDR within six months postpartum and 2270 controls. One case (0.4%) and eight (0.4%) controls were exposed to loratadine in the first trimester and up to 30 days before the time of conception. The adjusted odds ratio (OR) for hypospadias among users of loratadine relative to non-users was 1.4 (95% CI: 0.2-11.2) and the corresponding OR for other antihistamines was 1.9 (95% CI: 0.7-5.7). In this study, maternal exposure to loratadine did not appear to be associated with an increased risk of hypospadias when compared with other antihistamines, although it should be noted that the statistical precision of the risk estimates might be limited.

Key words: Hypospadias, Loratadine, pregnancy, drug safety, case-control studies

1. Introduction

Hypospadias occurs with a reported prevalence of 0.3% to 0.8% and since the 1970s, multiple reports from the United States, England, Scandinavia, and Hungary have shown an increase in the occurrence of hypospadias [1-7]. Although very few risk factors for hypospadias are established, gestational and pre-existing diabetes, intrauterine growth retardation, paternal subfertility, *in vitro* fertilization (IVF), maternal age, and genetic factors have all been suggested to be associated with an increased risk of hypospadias [8-17].

Loratadine is a non-sedating antihistamine commonly used for seasonal allergies [18]. In 2001, a report from Sweden suggested an association between maternal use of loratadine and infant hypospadias [19]. Having considered year of birth, maternal age, and parity, the odds ratio (OR) for hypospadias in relation to loratadine exposure was 2.39 (95% confidence interval [CI]: 1.43-3.38). The study also compared the occurrence of hypospadias after the use of other antihistamines. The OR for having a diagnosis of hypospadias in the Swedish Medical Birth Registry (MBR) after maternal use of loratadine compared with maternal use of other anti-allergic anti-histamines was 4.0 (95% CI:1.42-12.9) [19].

Neither a recent study from Israel including 210 pregnant women exposed to loratadine [20] nor a study that used data from four countries and included 161 pregnant women exposed to loratadine [21] found an increased risk of hypospadias. However, these studies had limited power and due to the low prevalence of hypospadias not one case could be expected. Recently, the American Centers of Disease Control and Prevention (CDC) reported a case-control study including 563 infants with second- or third-degree hypospadias [22]. This study did not find any association between loratadine use and hypospadias. But since first-degrees hypospadias was excluded CDC could not assess the potential association between the mildest form of hypospadias and loratadine. Since use of anti-allergic drugs is common, any causal association may have major public health implications. We, therefore, conducted a case-control study in Denmark based on hospital discharge data of cases with hypospadias and population controls linked to Danish prescription registries.

2. Materials and methods

Study population

The study was conducted in the four Danish counties of North Jutland, Aarhus, Viborg and Ringkoebing which account for 30% of the Danish population (~1.6 M). A total of 65,383 male births with a full prescription history of the mother were available for analyses in the study period from 1989-2002 (North Jutland n=34,859), 1996-2002 (Aarhus n=20,382) and 1998-2002 (Viborg n=4,148) and (Ringkoebing n=5,994).

Cases of hypospadias

We identified all cases of hypospadias in the period 1989-2003 from the nationwide Hospital Discharge Registry (HDR). This Registry comprises of data on all discharges from hospitals in Denmark and includes 10-digit personal identifiers, dates of admission and discharge, surgical procedures, and up to 20 diagnoses [23] classified according to the Danish versions of the International Classification of

Diseases, 8th Revision (ICD-8) until the end of 1993 and ICD-10 thereafter (ICD-9 was never used in Denmark). The codes for hypospadias in ICD-8 are 752.20 (hypospadia glandis, n=3), 752.21 (hypospadia corporis penis, n=1), 752.22 (hypospadia scrotalis, n=0), 752.28 (hypospadia alia definite, n=0), 752.29 (hypospadia, n=5); in ICD-10, the codes are Q54.0 (hypospadia glandis, n=101), Q54.1 (hypospadia corporis penis, n=11), Q54.2 (hypospadia penoscrotalis, n=0), Q54.3 (hypospadia perinealis, n=2), Q54.4 (hypospadia penis arcuatos, n=3), Q54.8 (other specified hypospadias, n=0), Q54.9 (hypospadias without any specifications, n=135); There were 159 children with multiple hypospadias codes, and 25 children with both ICD-8 and ICD-10 codes. Using these codes, a total of 319 cases of hypospadias were identified (anytime postpartum) in the cohort of 65,383 male births in the four counties.

The Danish Medical Birth Registry

The MBR, which comprises of data collected by midwives and doctors attending deliveries, contains information on all births in Denmark since 1 January 1973 [24,25]. The main data constitute maternal age, self-reported smoking status at first antenatal visit, birth order, stillbirth, Apgar score, gestational age, height and weight of the neonate, and personal identifiers for both mother and child [24].

Use of loratadine, other antihistamines, IVF drugs, antidiabetics and epileptics

As a part of the tax-funded healthcare for all inhabitants, the Danish National Health Service reimburses part of the patient expenditure on a wide range of prescribed drugs [21,26]. Danish patients are served by pharmacies equipped with electronic accounting systems that are used primarily to secure reimbursement for the National Health Service in each county. These systems include information on WHO's Anatomical Therapeutic Chemical (ATC) classification code, the amount of the drug prescribed, the personal identification number, and the date of drug dispension. Since January 1 1989 all data from North Jutland County have been stored in a prescription database maintained by the Department of Clinical Epidemiology, Aarhus University Hospital and since 2000 the Department of Clinical Epidemiology has also maintained similar research prescription databases from the three other counties. The data from these three counties are available from January 1, 1996 (Aarhus County) and January 1, 1998 (Ringkoebing and Viborg counties). Drugs sold over the counter are not available in these Prescriptions databases

Among cases and controls, prescriptions on loratadine (ATC codes: R06AX13), other antihistamines (ATC code: R06, except R06AX13), clomifene (ATC code: G03GB02), antidiabetics (ATC code: A10) and epileptics (ATC code: N03) was obtained from the prescription databases.

Data on preeclampsia

From the HDR we also obtained information on preeclampsia (ICD-8 codes: 637.03, 637.04, 637.09, 637.19; ICD-10 codes: 014, 015), since this has been found to be associated with hypospadias. The unique personal identifiers (CPR-numbers) were used to link records from all registries.

Statistical analysis

The association between use of loratadine and hypospadias was studied in a nested case-control design within the cohort of women who had a livebirth or a stillbirth after the 28th week of gestation. Use of loratadine was classified into three groups according to the time of exposure. The first trimester is considered the critical period for organ formation. Thus, the primary focus was the "early pregnancy" group, comprising of women who filled a prescription within 30 days before conception ("conception" was defined as the first day of last menstrual period [LMP]) up to the end of the first trimester (week 14 after the LMP). A second group comprised of women who filled a prescription within the first six months of pregnancy. A third group, the "entire pregnancy" group, comprised of women who filled prescriptions for loratadine at any time during pregnancy. Users of other antihistamines were classified similarly.

We restricted the first analysis to the pregnancies where the women lived in the four counties during the complete study period, which was the period between 30 days before conception and six months post-delivery. In the first analysis, cases were defined as boys with hypospadias recorded in the HDR during the first six months post-delivery.

The controls were selected from the study population of 65,383 male births. The control group comprised of 10 controls per case, and these controls had no recorded diagnosis of hypospadias during the first six months post delivery. We matched on birth, month, and year of the child. To examine whether the restriction of the hypospadias diagnosis to six months post-delivery had any impact on the results, we conducted a second analysis in which we defined cases as boys with hypospadias recorded in the HDR any time post-delivery (some children might have been coded later e.g. at the time of surgery) and controls as boys with no recorded diagnosis of hypospadias during the study period. In this analysis, cases and controls had to have lived in the four counties until the cases were diagnosed.

For the main study variables, we constructed contingency tables between exposure to loratadine, other antihistamines, case/control status and possible confounders. We used exact conditional logistic regression to estimate the relative risk by virtue of the OR of hypospadias associated with exposure to loratadine adjusted for maternal age, birth order, smoking status, preeclampsia, use of clomifene (a proxy for IVF), diabetes, and epilepsy. The analyses were done using SAS version 9.1 (SAS Inc., Cary, NC, USA).

3. Results

We identified 227 cases of hypospadias and 2270 matched controls when considering diagnosis within six months postpartum. Descriptive data for cases and controls are shown in Table 1. A total of one case and eight controls were exposed to loratadine in the first trimester or up to 30 days before the time of conception compared with four cases and 23 controls

exposed to other antihistamines in the first trimester or up to 30 days before the time of conception.

Table 2 shows the ORs for hypospadias associated with exposure to loratadine and other antihistamines according to the time of exposure. The adjusted OR for loratadine exposure within 30 days before conception and during the first trimester was 1.4 (95% CI: 0.0-10.5). The adjusted OR for other antihistamines was 1.9 (95% CI: 0.5-5.8). The crude and adjusted odds ratios were similar, suggesting that the variables we controlled for were no major confounders.

For the second group, who filled the prescription within the first six month of pregnancy, and the third, "entire pregnancy" group, the adjusted ORs for loratadine exposure were 0.8 (95% CI: 0.0-4.9) and 0.5 (95% CI: 0.0-3.3), respectively. The adjusted ORs for other antihistamines were 1.6 (95% CI: 0.3-5.5) and 1.0 (95% CI: 0.2-3.4), respectively.

Table 1. Characteristics of 227 cases of hypospadias recorded within six months postpartum and 2270 control subjects.

Variable	Cases *N* (%)	Controls *N* (%)
Exposure to Loratadine*	1 (0.4)	22 (1.0)
30 days before conception and first trimester	1 (0.4)	8 (0.4)
First trimester and second trimester	1 (0.4)	15 (0.7)
During pregnancy	1 (0.4)	21 (0.9)
Exposure to other antihistamines*	4 (1.8)	40 (1.8)
30 days before conception and first trimester	4 (1.8)	23 (1.0)
First trimester and second trimester	3 (1.3)	21 (0.9)
During pregnancy	3 (1.3)	30 (1.3)
Maternal age		
<25	41 (18.1)	319 (14.1)
25-30	99 (43.6)	1,036 (45.6)
>30	87 (38.3)	915 (40.3)
Birth order		
1	108 (47.6)	942 (41.5)
1+	119 (52.4)	1,328 (58.5)
Smoking 1991-2002		
Yes	51 (22.5)	524 (23.1)
No	156 (68.7)	1,571 (69.2)
Missing	20 (8.8)	175 (7.7)
Gestational age		
≥37 weeks	198 (87.2)	2,160 (95.2)
34-36 weeks	20 (8.8)	81 (3.6)
<34 weeks	9 (4.0)	29 (1.3)
Prescription for ovulation-inducing drugs	1 (0.4)	44 (1.9)
Maternal epilepsy	2 (0.9)	13 (0.6)
Maternal diabetes	1 (0.4)	8 (0.4)
Preeclampsia	13 (5.7)	48 (2.1)

*Exposure during pregnancy and 30 days before conception

Considering all cases of hypospadias recorded anytime post-delivery (*N*=319), the risk estimates did not change markedly. The adjusted OR for exposure to loratadine in the first trimester and 30 days before conception was 1.1 (95% CI: 0.0-7.7), and the OR for exposure to other antihistamines in the same period was 1.7 (95% CI: 0.5-4.7). The adjusted OR for exposure to loratadine within the first six months of pregnancy was 0.6 (95% CI 0.0-3.8) and for the entire pregnancy 0.5 (95% CI 0.0-2.7). The adjusted ORs for other antihistamines were 1.1 (95% CI: 0.2-3.7) and 0.7 (95% CI: 0.1-2.3), respectively. The risk point estimates were generally higher for other antihistamines than for loratadine.

Since we only had one exposed case, our dataset did not allow separate analyses of hypospadias as a single outcome or as an outcome in combination with other congenital malformations. Such an analysis might have been useful in order to examine the presence of surveillance bias, as hypospadias occur in clusters with other malformations in some children.

4. Discussion

The current study has shown that maternal exposure to loratadine does not appear to be associated with an increased risk of hypospadias compared with other antihistamines. In fact, the risk point estimates for hypospadias were higher with maternal exposure to other antihistamines compared with loratadine. Thus, our risk estimates do not corroborate the findings in the Swedish study [19] that initiated the hypospadias debate. However our risk estimates had limited statistical precision and an effect similar to that in the Swedish study cannot be ruled out entirely.

Table 2. The association between hypospadias recorded within six months postpartum and maternal use of antihistamines according to time of exposure, odds ratios (OR) and 95% confidence intervals (CI)

Time of exposure	Crude OR (95% CI)	*Adjusted OR (95% CI) 1989-2002	**Adjusted OR (95% CI) 1991-2002
Exposure 30 days before conception and first trimester :			
Loratadine	1.3 (0.0-9.3)	1.4 (0.0-10.6)	1.4 (0.0-10.5)
Other antihistamines	1.7 (0.4-5.2)	1.8 (0.4-5.3)	1.9 (0.5-5.8)
Exposure first and second trimester :			
Loratadine	0.7 (0.0-4.4)	0.7 (0.0-4.8)	0.8 (0.0-4.9)
Other antihistamines	1.4 (0.3-4.9)	1.4 (0.3-4.9)	1.6 (0.3-5.5)
Exposure during pregnancy :			
Loratadine	0.5 (0.0-3.0)	0.5 (0.0-3.2)	0.5 (0.0-3.3)
Other antihistamines	1.0 (0.2-3.3)	1.0 (0.2-3.3)	1.0 (0.2-3.4)

*Adjusted for maternal age, birth order, ovulation-inducing drugs, maternal epilepsy, maternal diabetes and preeclampsia.

**Adjusted for smoking, maternal age, birth order, ovulation-inducing drugs, maternal epilepsy, maternal diabetes and preeclampsia.

Our case-control study had complete and independent registration of birth, birth outcome, and prescription data which prevented selection bias and some types of information bias; since the study was based on routinely recorded data, independent of the diagnosis. Importantly, there was no risk of recall bias, which can invalidate case-control studies that solely rely on interviews [27]. Although smaller than the Swedish Birth Registry, the database we used is one of the largest in the world for studying the safety of drugs used in pregnancy and previous studies have shown high data quality in both the prescription database and the Birth Registry [25,28]. Coding errors occur in less than 0.5 percent of cases in the prescription database [28].

Our study was based on the HDR, and it is known that discharge diagnoses listed in discharge registries are not always accurate. We reviewed 43 records of the hypospadias cases in our study and

found only three to be misclassified. Generally, lack of specificity, biases risk estimates towards unity. However, our prevalence of hypospadias corresponds to the prevalence reported in other datasets.

Loratadine is also sold "over the counter" in Denmark and since the prescription databases do not capture information regarding "over the counter" medication, the exposure information may be incomplete. Incomplete exposure information in the current study may bias the results towards unity as well.

Because of our reliance on dispensing information in the record linkage study, we do not know whether the women in the study actually took the drugs. However, the fact that patients are required to pay partially for the costs themselves is likely to have improved compliance.

We were able to adjust for possible confounding factors except for the years 1989 and 1990, where we did not have information regarding smoking. However, in our study, adjustment for the available confounding variables did not change the unadjusted risk estimates substantially, implying that these variables were no major confounders. Since the development of the external organs is initiated in the early fetal period, some of the studied variables such as preeclampsia should be interpreted as biological characterization of infants born with hypospadias rather than possible causal factors.

Our data are in line with the few other existing studies. Thus, in a recently conducted study by the CDC no association between maternal use of loratadine and second- or third-degree hypospadias was demonstrated [22]. Similarly, in an Israeli study [20], no increased risk of hypospadias was demonstrated in the loratadine group compared with other antihistamines. Moretti and coworkers found in a multi center study [21] that maternal exposure to loratadine was not associated with major malformations.

However, the infrequent maternal use of loratadine and the prevalence of hypospadias have a major impact on sample size requirements for providing the definitive assurances of the safety of loratadine to the unborn child [29]. Thus, to rule out a doubling of the risk of hypospadias would, based on our registries, require a study with 1,350 cases of hypospadias and 13,500 controls (power 80 percent and 0.5% exposure prevalence among controls).

5. Conclusion

In conclusion, maternal exposure to loratadine does not appear to be associated with an increased risk of hypospadias compared to other antihistamines. However, the statistical precision of our risk estimates was limited.

Conflict of interest

See Acknowledgements.

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Loratadine During Pregnancy and Hypospadias

To the Editor:

In November 2001, 2780 infants exposed to loratadine in utero were identified in The Swedish Medical Birth Registry. Among those infants were 15 cases of hypospadias, compared with 5.6 cases expected (based on a population rate of 1 case per 500 in the general population). The adjusted odds ratio for hypospadias and loratadine exposure was 2.4 (95% confidence interval = 1.4–3.4).[1] Continued monitoring suggested that the association was not readily consistent with occurrence by chance. Recently, the Swedish group[2] repeated the analysis for the period 2002–2004 and reported a prevalence ratio of 0.47 (0.06–1.65), a value considerably lower than their earlier report. This new analysis was based on 1911 infants exposed to loratadine in early pregnancy. Other attempts to study this relationship have been hampered by insufficient data and inconsistent results.[3–5]

To examine this association, we conducted a large nationwide case-control study in Denmark, based on administrative medical health databases and linkage to the Danish nationwide prescription database. We identified all boys with hypospadias in Denmark born in the period 1996–2004 from the nationwide Hospital Discharge Registry covering all Danish hospitals. The codes for hypospadias in ICD-10 are Q54.0 (n = 640), Q54.1 (n = 173), Q54.2 (n = 41), Q54.3 (n = 9), Q54.4 (n = 48), Q54.8 (n = 10), Q54.9 (n = 654). Using these codes, a total of 1575 cases of hypospadias were identified anytime after delivery. For each case we randomly selected from the Danish Medical Birth Registry up to 10 controls (live male births) without a diagnosis of hypospadias, matched by birth year and mother's residence. Through the nationwide prescription database, maintained by The Danish Medicines Agency, we identified all prescriptions to the mothers of cases and controls before the date of birth.

We used conditional logistic regression to estimate prevalence ratios, controlling for potential confounding factors obtained from the databases, including maternal age, smoking status, birth order, preeclampsia, and prescriptions for ovulation-inducing drugs, antidiabetics, and antiepileptics (Table).

We found a negative association between maternal exposure to loratadine and prevalence of hypospadias. Among 1575 cases of hypospadias, 7 cases (0.4%) and 88 controls (0.6%) were exposed to loratadine in the 30 days before conception and during the first trimester. The adjusted prevalence ratio for hypospadias among users of loratadine relative to nonusers was 0.6 (95% CI = 0.3–1.4) and the corresponding prevalence ratio for other antihistamines was 1.3 (0.9–1.9). The adjusted prevalence ratio for hypospadias among users of loratadine during the entire pregnancy relative to nonusers was 0.9 (0.5–1.6) and the corresponding prevalence ratio for other antihistamines was 1.0 (0.7–1.5).

Thus, in this large population-based nationwide study, we found strong evidence that maternal exposure to loratadine does not substantially increase the risk of hypospadias. Our findings do not corroborate the first Swedish study[1] that initiated the hypospadias debate, but they are consistent with the other small studies that have reported on this topic.[3–5] Several factors should be taken into account when interpreting this study. The full and independent nationwide registration of births, malformations, and prescriptions prevented several types of bias. Any noncompliance with the use of antihistamines and inaccurate data in the databases might bias the estimates of risk towards the null, since this imperfect specificity in routinely recorded data is most likely independent of prescription information.

TABLE. Characteristics of 1575 Cases of Hypospadias Recorded Anytime Postdelivery and 14,660 Control Subjects

	Cases No. (%)	Controls No. (%)	Unadjusted PR (95% CI)	Adjusted PR (95% CI)*
Exposure 30 d before conception and during first trimester				
Loratadine	7 (0.4)	88 (0.6)	0.7 (0.3–1.6)	0.6 (0.3–1.4)
Other antihistamines	28 (1.8)	217 (1.5)	1.2 (0.8–1.8)	1.3 (0.9–1.9)
Exposure anytime during pregnancy				
Loratadine	15 (1.0)	148 (1.0)	0.9 (0.5–1.6)	0.9 (0.5–1.6)
Other antihistamines	36 (2.3)	345 (2.4)	1.0 (0.7–1.4)	1.0 (0.7–1.5)

*Adjusted for maternal age, smoking status, birth order, preeclampsia, prescription for IVF, antidiabetics, or antiepileptics.

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Confounding in Database Pharmacoepidemiology Studies

To the Editor:

Database studies are an important part of observational epidemiologic drug research, but there are limitations with this approach. Concerns have been expressed over potential differences in data availability between clinical databases (based on physician records)[1] and prescription claims databases (based on requests for reimbursement for medical services).[2] Also, all database studies are potentially subject to confounding bias due to drug channeling.[3] We illustrate the possible impact of these issues using an example of antithrombotic medications and the risk of gastrointestinal bleeding.[4]

Our example is a nested case-control study[5] conducted within the United Kingdom General Practice Research Database from 2000 through 2005. In this study, 4028 cases of gastrointestinal (GI) bleed were matched on index date to 40,171 controls.[4] Index date was the date of the first GI bleed. Drug exposure was measured by a prescription issued in the 90 days before the index date. Using a nested case-control design allows us to estimate the rate ratios (RRs) of these exposures on the outcome.[5]

We compared the sensitivity of the RR estimates of exposure to warfarin, clopidogrel, or aspirin on bleeding when including or excluding the following lifestyle variables from the analysis: smoking, drinking, body mass index, and blood pressure. We broadly adjusted for covariates (such as comorbid conditions) that are potential risk factors for the outcome and would be available in both types of databases.[4]

Drug channeling was assessed using the controls from the case-control study as a subcohort. Exposure to either warfarin or clopidogrel was evaluated for its association with subsequent prescriptions for nonaspirin nonsteroidal antiinflammatory drugs (NSAIDs) because coprescription of these drugs would put a subject at a higher risk of a bleed due to drug–drug interaction.[4]

Lifestyle variables were important predictors of the study outcome with the strongest association being between GI bleed and heavy alcohol use (RR = 4.0; 95% confidence interval [CI] = 3.45–4.63).

Table 1 shows the estimates of the effect of exposure to antithrombotic agents on the risk of GI bleed. Estimates are similar regardless of the inclusion or exclusion of lifestyle variables in the regression analysis. The largest change in any parameter estimate was with aspirin where the additional adjustment for lifestyle variables produced an 8% difference in the parameter estimate for GI bleeds among the exposed.

The rate of coprescription of NSAIDs and warfarin was lower than would be expected by chance alone. After adjusting for age and sex, being prescribed clopidogrel had no effect on the rate of NSAID prescriptions (RR = 0.97; 95% CI = 0.74–1.27). In contrast, warfarin users were much less likely to be prescribed an NSAID (0.44; 0.34–0.56). We observed similar effects on the rate of aspirin prescription for clopidogrel users (1.00; 0.82–1.22) and warfarin users (0.22; 0.18–0.28), but this difference is harder to interpret, because aspirin is often coprescribed with clopidogrel following angioplasty as benefits clearly outweigh risks in this situation.[6]

Drug channeling for warfarin is present in this population, and this channeling needs to be considered when interpreting estimates of bleeding. These results suggest that NSAIDs are being channeled away from warfarin users, implying that these risk estimates are too conservative.

However, in assessing the bleeding risks associated with exposure to these drugs, estimates were not sensitive to the omission of lifestyle variables. It is well known that strong unmeasured confounding can potentially create an exposure–disease relationship.[7] However,

TABLE 1. Association of Being Prescribed Warfarin, Aspirin, or Clopidogrel With the Rate of Gastrointestinal Bleeds

Agent	Cases (n = 4028)	Controls (n = 40171)	Adjusted (All Data) RR (95% CI)	Adjusted (No Lifestyle Variables)* RR (95% CI)	% Change in Parameter Estimate†
None‡	2589	31,380	1.00	1.00	n/a
Warfarin	281	1130	2.12 (1.77–2.54)	2.09 (1.75–2.50)	1.6
Clopidogrel	160	532	2.08 (1.67–2.59)	2.12 (1.71–2.64)	2.9
Aspirin	1122	7350	1.55 (1.41–1.71)	1.61 (1.47–1.75)	8.0

Estimates are with and without variables typically unavailable in prescription claims databases.
*Here we omit the clinical database variables of smoking, body mass index, alcohol use, and blood pressure (variables absent in prescription claims databases) as covariates from the adjusted regression estimates.
†This is the parameter estimate of the log rate ratio (RR).
‡Reference category.

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